

# THE CHEMISTRY OF ORGANIC COMPOUNDS



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# The Chemistry of Organic Compounds

A Year's Course in Organic Chemistry

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## PREFACE

In the six years which have elapsed since the publication of the first edition of this book, organic chemistry has advanced on many fronts. A thorough and extensive revision of a textbook therefore presents many problems. The treatment of the subject must be brought up to date not only in order to insure the accuracy of all statements but in order that the student may see at least from a distance where the battle now rages. Recent discoveries have undoubtedly a pedagogic value by virtue of the fact that they are recent. This is particularly true if these new developments have either industrial or biological implications. The trend of research in organic chemistry during the last decade has been more and more in the direction of either biological chemistry or in the application of physical chemistry to the study of organic reactions. In adding new material we have had this trend in mind. However, we have neither overlooked the industrial advancements, nor the development of those new organic reactions which are rapidly finding application in synthetic and structural research. To find space for the new additions, certain sections of the first edition have been condensed and the consideration of a few subjects omitted.

Since it is of the utmost importance that a beginner be introduced to this complex science by slow stages, we have not condensed the rather extensive exposition of the basic principles characteristic of the first dozen chapters of the first edition. We have continued to stress the experimental basis of the structural theory; we have sought to show the student how to use his knowledge in solving simple problems of structure and synthesis. The seventh chapter, which deals with methods of determining structure and with methods of synthesis, has been retained with a few corrections and additions because it provides an opportunity of reviewing the fundamental principles presented in the first six chapters.

In this new edition the nitriles are considered together with the amines and amides. The separate chapter on hydrocyanic acid is omitted. Space is thus saved without eliminating important material. Throughout the revision we have tried to balance the

importance of each portion of the material characteristic of the usual elementary textbook against the significance to the student of such new developments as the elucidation of the structure of the sterols. With an increase in the number of pages of only five per cent we have thus succeeded in including much new material on the hormones, vitamins, sugars, proteins, and certain other substances of importance to the biochemist.

A consideration of alicyclic compounds has been postponed until after the aromatic polynuclear compounds have been treated. This arrangement was essential if the chemistry of the sterols and bile acids was to be considered. Quite apart from the biochemical and medical significance of many substances containing a hydrogenated phenanthrene nucleus, they afford an excellent medium by which the student may become familiar with the use of relatively simple reactions in the study of complex compounds. This chapter is full of illustrations of special uses of general reactions of aliphatic chemistry. It also provides some interesting examples of a type of stereoisomerism which we have elaborated in the introductory chapter (XXVI) on alicyclic compounds.

Our use of the electron theory of valence which in the first edition centered around the chemistry of nitrogen compounds has been extended. The concept of resonance is introduced in connection with the study of the guanidinium ion. We have made repeated use of this idea in treating aromatic compounds in the later portions of the book. The approach to this difficult subject has been experimental rather than theoretical. We have made no attempt to explain wave-mechanics, but we have emphasized the non-existence of electronic isomers which correspond to the two Kekulé formulas for benzene derivatives and the several structures which may be written for a substituted guanidinium ion. The student's attention is repeatedly drawn to the fact that associated with the absence of electronic isomers is increased stability of the molecule as shown by shortened inter-nuclear distances (X-ray analysis) and by the energy relationships (basic or acid strength and heats of formation).

The chapter on heterocyclic compounds (Chapter XXVIII) is essentially new. It is an attempt to present in brief the fundamental principles of this extensive and varied class of substances from the point of view of their behavior and methods of synthesis. The idea of resonance energy and the distinction between aromatic

and partially hydrogenated aromatic compounds seem to us helpful guides through this complex field. The following chapter on drugs (XXIX) makes use of the more important reactions included in this general chapter. In dealing with both aromatic heterocyclic compounds and polynuclear aromatic homocyclic compounds we have employed formulas in which the double linkages in the rings are shown. In the case of benzene and its derivatives, on the other hand, we have employed the conventional outline formula. We believe this distinction is sound as a practical matter, though we have taken pains to point out to the student (p. 454) the problem that is involved in attempting to decide where to place the symbols for unsaturation in aromatic rings. The formulas we have employed for such compounds as naphthalene and phenanthrene derivatives, for example, correspond to certain experimental facts connected with the behavior of these substances. On the other hand, to write similar formulas with double bonds for such benzene derivatives as ortho cresol, is not possible; in this series there are no reactions which may be regarded as characteristic of one of the two isomeric arrangements of double linkages.

A brief résumé of the evidence for the size of the ring in simple sugar derivatives has been included in the chapter on carbohydrates. The stereochemical treatment of the sugars is still kept in the concluding chapter. Many teachers may wish to turn to this portion of the book while studying Chapter XVII. Others may feel that if time is limited other material is more important in these days despite the time-honored tradition of requiring students to memorize the methods of determining the configuration of the pentoses. The recent success which has attended the study of Walden's inversion seemed to warrant a more extended treatment of this subject in the last chapter; this will, however, probably be read only by advanced students. The last two chapters, in particular, provide ample opportunity for a choice of topics, since with them the book includes more material than could be covered normally in one year.

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February 16, 1939

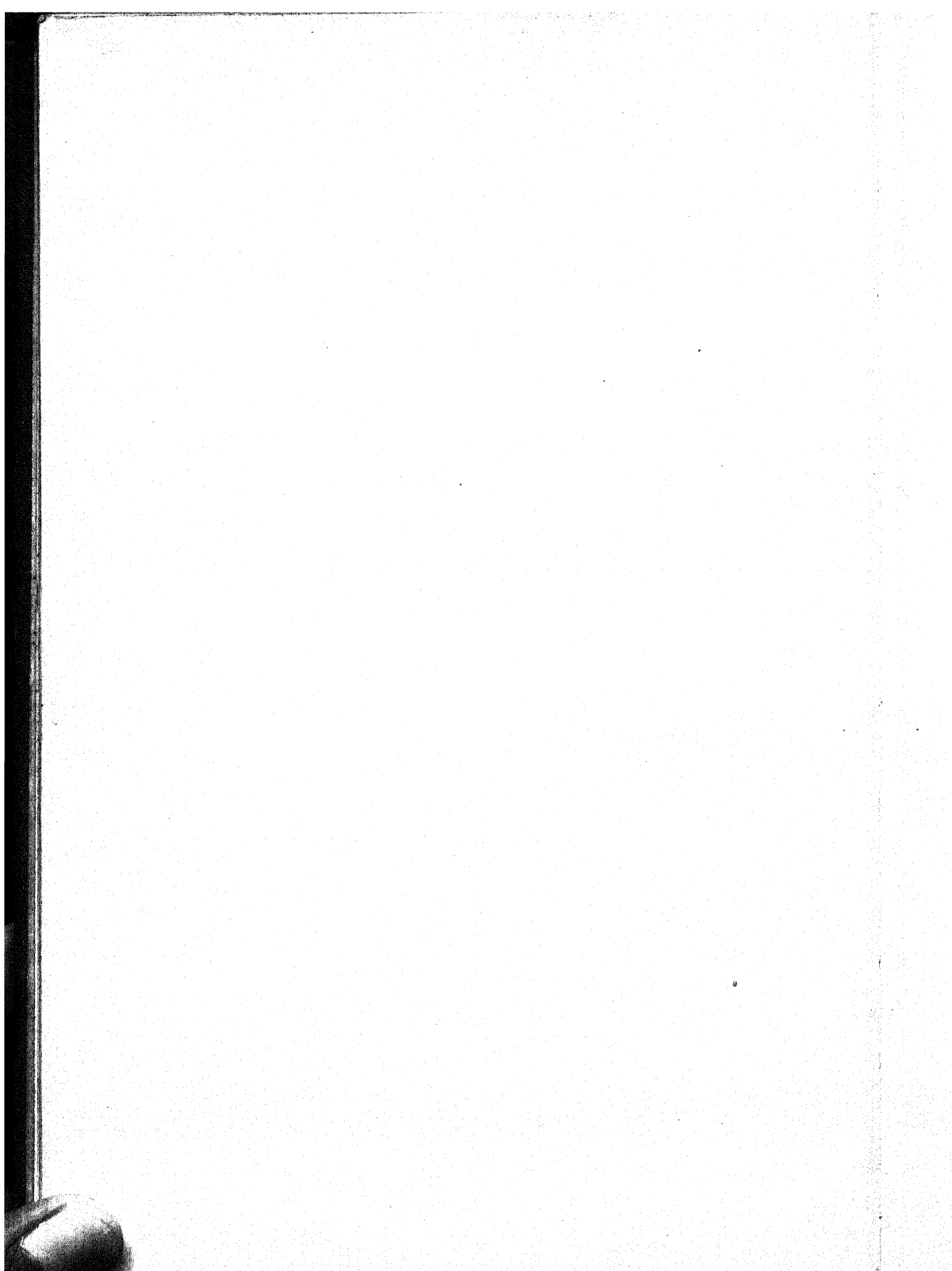


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# THE CHEMISTRY OF ORGANIC COMPOUNDS



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## FOREWORD

Organic chemistry is the chemistry of the compounds of carbon. At first sight, it seems strange that one element should be singled out for special attention, and stranger still, perhaps, that this branch of chemistry should be considered important enough to be one of the two major divisions of the subject. No other element shares this honor with carbon; all the rest of chemistry is classed together under the one heading, — inorganic chemistry.

The origin of the name suggests one of the reasons for the importance of organic chemistry: originally the science dealt with the products of plant and animal life. It was long believed that these were in some mysterious way different from the lifeless rocks and minerals with which inorganic chemistry dealt. The distinction was shown to be false by the synthesis from inorganic materials of several natural products. This barrier between the two chemistries was thus broken down and it was recognized that the fundamental laws and principles of both were identical. Since almost all the important substances produced by animate nature contain carbon, the name organic chemistry was transferred to the study of the compounds of this element.

Thus, from its earliest beginnings to the present, organic chemistry has been closely associated with the study of life itself. In many cases it is impossible to mark off organic chemistry from biochemistry, and this, in turn, from physiology. For this reason, a knowledge of organic chemistry has been indispensable to progress in many branches of biology. The connection with medicine has been twofold: on the one hand, through physiology and physiological chemistry, on the other, through pharmacology. The organic chemist's study of such natural drugs as cocaine has led to the synthesis of simpler substances with similar or superior pharmacological action. Today in many medical schools, hospitals and research institutes, the doctor, the phys-

iologist and the organic chemist are coöperating in a study of the varied problems confronting the medical profession.

From physiology to the coal tar dye industry seems a far cry, but it is not so in reality. Coal tar is a mixture of carbon compounds; from them the chemist has prepared a multitude of new substances of scientific and practical importance. At his bidding, the new coal tar dye industry sprang up. It now supplies practically all the dyes in use and, in addition, many drugs, perfumes, flavors, photographic developers and high explosives. The study of these synthetic coal tar products has gone hand in hand with the investigation of plant and animal substances. Knowledge gained in the one field has been applied to the other, often by the same man. The most distinguished organic chemist of the last generation, Emil Fischer, was able to make rapid progress in the study of the sugars largely because of a discovery made in an investigation of certain compounds prepared from coal tar. He will be remembered for the investigation of varied natural products and also as a pioneer in the study of coal tar dyes.

In listing the important aspects of organic chemistry, petroleum must not be overlooked. This complex mixture of organic compounds has yielded primarily fuel, at first for lamps, and now for the internal combustion engine and the oil-burning steam engine. The organic chemistry of this raw material was slow in developing. But today, a number of new and useful compounds are being prepared from petroleum and natural gas.

From an industrial point of view, the chemistry of plant and animal products is also important. The production of automobile tires from rubber, a complex plant product, is an enormous chemical industry in itself. The manufacture of many common substances, such as vinegar, soap, corn syrup and "vegetable fats" (hydrogenated oils) are examples of applied organic chemistry. So also is the transformation of cotton into artificial silk, automobile varnish, moving picture films and smokeless powder.

Many of those who make the acquaintance of organic chemistry on their way to other callings will be impressed chiefly by the applications of the science to medicine or to technology. The success and importance of these applications loom large in the public eye, and the organic chemist has reason to be proud of them. He knows, however, that they would have been impossible if the science itself had not developed in a rather remark-

able and spectacular way in the last part of the nineteenth century, and continued to expand on the sure foundations which were then laid. This science seems to many a more remarkable achievement of the human brain than its technical applications. The two cannot really be separated, however, as even an elementary study of the subject will demonstrate. Both have been kept in mind in the writing of this book in order to give a true picture of the varied and fascinating ramifications of organic chemistry.

## CHAPTER I

### THE ALCOHOLS

**Composition of Ethyl Alcohol.** Ethyl alcohol is a substance of such great practical importance that we may well choose it as the starting point in a study of organic chemistry. Later, we shall consider its industrial significance and the commercial methods of preparation. For the present, let us center our attention on a chemical investigation of its constitution. The first step in such a study involves the careful purification of the compound, and the second, the qualitative and quantitative analysis. A discussion of these fundamental methods will be found in a laboratory manual of organic chemistry and we may therefore turn directly to the results. Pure ethyl alcohol is a liquid boiling at  $78^{\circ}$ ; a quantitative analysis shows that it contains carbon, hydrogen and oxygen in such amounts as correspond to the existence of two carbon atoms, six hydrogen atoms and one oxygen atom.

#### THE DETERMINATION OF THE EMPIRICAL FORMULA OF ETHYL ALCOHOL

##### *Results of Quantitative Analysis*

ELEMENT	PER CENT	ATOMIC WEIGHT	ATOMIC RATIO	RATIO OF ATOMS
Carbon	52.18	$\div 12$	$= 4.35$	$4.35 \div 2.17 = 2$
Hydrogen	13.04	$\div 1$	$= 13.04$	$13.04 \div 2.17 = 6$
Oxygen	34.78	$\div 16$	$= 2.17$	$2.17 \div 2.17 = 1$

The **empirical formula** is therefore  $C_2H_6O$ . Such a formula tells us only the relative number of atoms in the molecule. To establish the **molecular formula** of a compound it is necessary to have information in regard to the molecular weight. A determination of the molecular weight (the third step in the investigation) is readily accomplished by finding the density of the vapor.<sup>1</sup>

<sup>1</sup> The molecular weight may also be determined by noting the depression in the freezing point (or elevation in the boiling point) of a suitable solvent in which a weighed amount of the substance has been dissolved. The principle of this method is explained in textbooks of elementary general chemistry.

The results of many such experiments have shown that the molecular weight of ethyl alcohol is 46. The molecular formula of ethyl alcohol is therefore  $C_2H_6O$  ( $2 \times 12 + 6 + 16 = 46$ ).

**Isomerism.** In an elementary study of inorganic chemistry we should hail this result with satisfaction, since the determination of the kind and number of atoms in the molecule is usually sufficient to establish an adequate formula; for example  $NH_3$ ,  $HCl$ ,  $H_2O_2$ . These are called molecular formulas. Quite the contrary is the case in organic chemistry: such formulas are inadequate in dealing with the compounds of carbon. This may be illustrated by a simple example. **Methyl ether**, a gas related to the ether used in anesthesia, has exactly the same percentage composition and the same molecular weight as ethyl alcohol. Therefore it must be also represented by the formula  $C_2H_6O$ . There can be no doubt about the difference between these compounds, since one is a liquid boiling at  $78^\circ$  and is soluble in water, while the other is a gas at room temperature and is insoluble in water. Their chemical reactions are also entirely different. *Two compounds which have the same molecular formula are said to be isomers; the phenomenon is known as isomerism.*

**The Necessity for Structural Formulas.** Isomerism is very common in organic chemistry. For example, twenty-six isomers with the formula  $C_6H_{14}O$  have been prepared and their properties recorded. It is obvious that unless the organic chemist is able to write formulas which represent the differences between isomers, he is in a hopeless position. It was not until about the middle of the last century that a satisfactory method of formulating organic compounds was developed; before this time the chemistry of the carbon compounds was in a confused state. After the introduction of structural formulas, organic chemistry advanced by leaps and bounds. The chief name associated with the remarkable advancement in this field of chemistry is that of Kekulé.<sup>1</sup>

**The Theory of Linkages.** The theory which was advanced to explain the differences between the various isomers may be called the theory of atomic linkages. This assumes that isomerism is due to the different ways in which the same atoms are joined together in the molecule. The organic chemist, thus, seeks to express in his structural formulas not only the number and kinds

<sup>1</sup> Friedrich August Kekulé (1829-1896). Professor of Chemistry at the University of Bonn.

of atoms in the molecule but *the way in which they are linked together*. In other words his formulation must represent the structure of the compound. Let us see how this may be done in the case of ethyl alcohol.

**Hydroxyl Group in Alcohols.** Ethyl alcohol is very similar to water in many of its chemical properties, as is illustrated by the following reactions with metallic sodium and phosphorus trichloride:

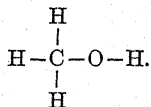
1. (a)  $2\text{H}_2\text{O} + 2\text{Na} \longrightarrow 2\text{HONa} + \text{H}_2$ ,  
 (b)  $2\text{C}_2\text{H}_5\text{O} + 2\text{Na} \longrightarrow 2\text{C}_2\text{H}_5\text{ONa} + \text{H}_2$ ,
2. (a)  $3\text{H}_2\text{O} + \text{PCl}_3 \longrightarrow 3\text{HCl} + \text{P}(\text{OH})_3$ ,  
 (b)  $3\text{C}_2\text{H}_5\text{O} + \text{PCl}_3 \longrightarrow 3\text{C}_2\text{H}_5\text{Cl} + \text{P}(\text{OH})_3$ .

It will be noticed that in the first two reactions, sodium hydroxide and a compound,  $\text{C}_2\text{H}_5\text{ONa}$  (sodium ethylate), are formed by the replacement of one hydrogen of the molecule. In the second set of reactions, the phosphorus atom becomes attached to an hydroxyl group which in one case has been removed from water and in the other must come from the alcohol. The facts of inorganic chemistry show that the atoms in the water molecule must be arranged  $\text{H}-\text{O}-\text{H}$ ; the existence of the hydroxyl group ( $\text{OH}$ ) is evident. Since the phosphorous acid is formed from alcohol as well as from water (equations 2a, 2b), we may conclude with considerable assurance that *ethyl alcohol has an hydroxyl group*.

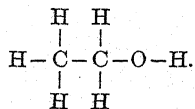
These two reactions are also characteristic of another well-known substance, — **methyl alcohol**. This compound (commonly called **wood alcohol**) has the molecular formula  $\text{CH}_4\text{O}$  as determined by the analysis and vapor density of a carefully purified sample. Since it reacts with sodium evolving hydrogen, and with phosphorus trichloride forming phosphorous acid,  $\text{P}(\text{OH})_3$ , we conclude that it also contains an hydroxyl group. We may, therefore, write the formulas  $\text{CH}_3\text{OH}$  for methyl alcohol and  $\text{C}_2\text{H}_5\text{OH}$  for ethyl alcohol. These formulas, however, are still not perfectly clear. How are the carbon and hydrogen atoms arranged in the groups  $\text{CH}_3$  and  $\text{C}_2\text{H}_5$ ?

**Structure of Methyl and Ethyl Alcohols.** The founders of the structural theory have assumed that in organic compounds carbon always has a valence of four, oxygen of two, and hydrogen of one. With this as a basis the question raised concerning the structure of methyl alcohol is easily answered. *There is only one possible*

arrangement of the atoms in  $\text{CH}_3\text{OH}$ , and that is, the three hydrogen atoms must be attached to the lone carbon and this, in turn, must be bound to the hydroxyl group. Thus we have a complete structural or graphical formula:



The dash (—) whether vertical or horizontal stands for a valence bond, a link, which joins the atoms together. There are four bonds from the carbon atom, two from the oxygen atom, and only one from each hydrogen atom. Applying the same principles, the complete structural formula of ethyl alcohol is:

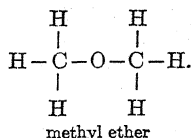


By attempting to write a variety of structural arrangements for ethyl alcohol it is easy to convince oneself that there is only one way of writing  $\text{C}_2\text{H}_5\text{OH}$ , *provided* that the valence of hydrogen is one, oxygen two, and carbon four. It is, of course, immaterial whether the formula be written from right to left or left to right or at what angle the various atoms are connected. The structural formula simply says that the two carbon atoms in ethyl alcohol are joined to each other, and that one is attached to three hydrogens, the other to two hydrogen atoms and the hydroxyl group.

**Writing Structural Formulas.** A study of a great variety of organic compounds has made certain the original assumption in regard to the valence of carbon, oxygen and hydrogen. Carbon always has a valence of four, except in a few very unusual substances. Therefore, in writing structural formulas we must arrange the atoms in such a way that each carbon atom always is connected with four linkages, oxygen with two, and hydrogen with one. *Every formula should be tested by noting the valence of each atom.*

**Structure of Methyl Ether.** Methyl ether, spoken of above as the isomer of ethyl alcohol, reacts neither with phosphorus tri-chloride nor with sodium; therefore, it has *no* hydroxyl group.

It has the following formula, which, it is easy to see, represents a molecule of an entirely different nature from that of ethyl alcohol. This case of isomerism is thus explained satisfactorily by the structural theory:

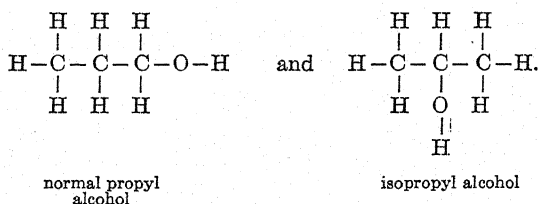


**The Alcohols as a Class of Compounds.** Besides the well-known methyl and ethyl alcohols, there are a great many other substances which are called alcohols by the organic chemist. They all show the reactions which we have learned are characteristic of an hydroxyl group, and their structural formulas, therefore, must show the linkage  $-\text{O}-\text{H}$ . They form a graded series with an increasing number of carbon atoms. Such a series of compounds is called an *homologous series* and is illustrated below.

NAME	GENERAL FORMULA	DIFFERENCE	NUMBER OF ISOMERS
Methyl alcohol	$\text{CH}_3\text{OH}$	$\text{>CH}_2$	one substance
Ethyl alcohol	$\text{C}_2\text{H}_5\text{OH}$	$\text{>CH}_2$	one substance
Propyl alcohols	$\text{C}_3\text{H}_7\text{OH}$	$\text{>CH}_2$	two substances
Butyl alcohols	$\text{C}_4\text{H}_9\text{OH}$	$\text{>CH}_2$	four substances
Amyl alcohols	$\text{C}_5\text{H}_{11}\text{OH}$	$\text{>CH}_2$	eight substances

We may define an homologous series as a series of similar compounds in which *each member differs from the one below it and the one above it by  $\text{CH}_2$* . It will be noted that all the compounds of this series correspond to a general formula  $\text{C}_n\text{H}_{2n+1}\text{OH}$ . That is, the number of hydrogen atoms (not including that of the OH group) is one more than twice the carbon atoms.

**Isomeric Propyl and Butyl Alcohols.** When we come to the substance  $C_3H_7OH$  in the homologous series of alcohols, we find that *more than one substance is represented by the formula*. In other words, a still more subtle type of isomerism is now at hand. The reason for this is evident from a consideration of the complete structural formulas of such substances. Bearing in mind the rules in regard to the valence of the different atoms and the fact that the substances all contain one hydroxyl group, we find that there are two and *only two* ways of arranging the atoms in  $C_3H_7OH$ ; these are:

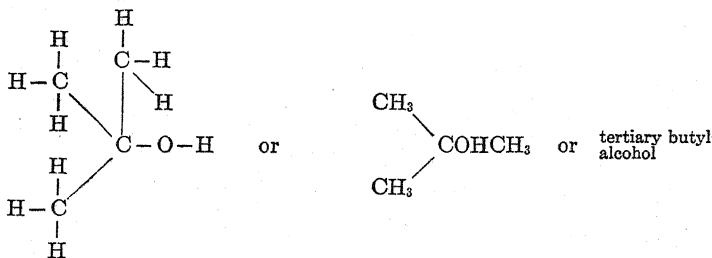
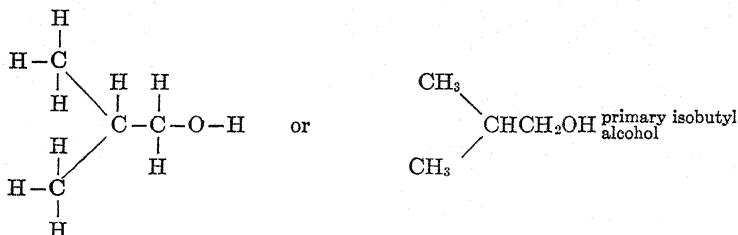
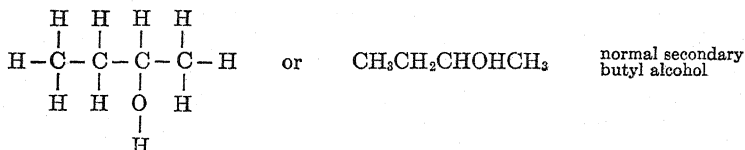
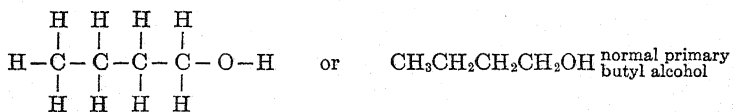


These formulas are usually written as  $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$  and  $\text{CH}_3\text{CHOHCH}_3$ . There are actually two and *only two* substances  $C_3H_7OH$ ; one is normal propyl alcohol boiling at  $98^\circ$ , the other is isopropyl alcohol which boils at  $82^\circ$ .

At first sight it might appear that there were many different ways of arranging the atoms in the molecule  $C_3H_7OH$ , all of which conformed to the rules of valence. That this is not the case, perhaps becomes convincingly demonstrated only by actual trial with a pencil and paper. It will be remembered that the linkage of two carbon atoms through oxygen is excluded from the possibilities by the fact that the compound has an hydroxyl group (it is an alcohol). Hydrogen has only one valence bond and therefore can not serve to join two other atoms together. Therefore the three carbon atoms must be joined in a chain. The position of the hydroxyl group is the only variable left. This group may be placed at the right end, in the center or at the left end. The seven hydrogen atoms of  $C_3H_7OH$  now will be found sufficient to occupy the seven remaining bonds of the three carbon atoms. A moment's consideration will convince one that there is no difference between the two ends of this symmetrical chain of carbon atoms. Whether the hydroxyl group is written at the left end or the right end is without significance. Both arrangements represent the same linkage, — they could be cut out and superimposed on each other by merely turning through  $180^\circ$ . The arrangement with the hydroxyl group in the center is different. This can not be superimposed on the other formula because the hydroxyl group is attached to a carbon atom in the middle of the chain. Thus, in one formula we have the group  $\text{>CHOH}$ , in the other  $-\text{CH}_2\text{OH}$ .

# 10 THE CHEMISTRY OF ORGANIC COMPOUNDS

The isomerism of the butyl alcohols,  $C_4H_9OH$ , is represented by the following structural formulas:



Thus, with the aid of the structural theory, we can predict the number of isomers which are possible in the case of the propyl alcohols and butyl alcohols, and test the prediction by experiment. Repeated trials in many laboratories have shown that such predictions of the structural theory are always verified. By working long enough and hard enough, it is always possible to make the number of isomers required by the theory, but more than this number have never been found. Since the number of isomers increases very rapidly as one goes up an homologous series, many isomers of the higher members have not yet been prepared. However, since our experimental facts and the predictions of the structural theory coincide so precisely in the case of the lower

members of this and other series, we feel perfectly confident that in time exactly the number of isomers demanded by the theory could be prepared in each case.

**Conventions Used in Writing Formulas.** As a matter of convenience, organic chemists have agreed to write their structural formulas in a condensed form, and the student would do well to master the conventions employed. The extended formulas of the butyl alcohols which are printed on page 10 on the left (sometimes called spider web formulas) are often useful at first in understanding the theory of linkages, but the student should use them as little as possible. The conventions used will be apparent from these examples; the usual formula is printed on the right. It should be noted that we write the group of carbon and hydrogen atoms after each other in straight chain compounds and show their connection by bonds in branched chain compounds; other groups or atoms follow the hydrogen.

**Naming Alcohols.** Since there are only two isomeric propyl alcohols, it is possible to refer to them by using the terms *normal* and *iso*. By using the word *normal* to indicate a straight chain (abbreviated by *n*-, thus *n*-propyl alcohol) and *iso* to denote a forked chain, a fairly satisfactory method of naming the butyl alcohols can also be developed. Furthermore, an examination of the various butyl alcohols will show that they can be arranged into the three following groups: (1) those having the grouping  $-\text{CH}_2\text{OH}$  which are called **primary** alcohols; (2) those having the grouping  $\text{>CHOH}$  which are called **secondary**; (3) those with the grouping  $\text{>COH}$  which are designated as **tertiary** alcohols. We shall postpone any considerations of a more complete system of naming the alcohols until the next chapter.

The names of the first five normal straight chain alcohols are those given in the tables below and on page 10. The alcohols with six or more carbon atoms are named with a Greek prefix indicating the number of carbon atoms. For example, the normal alcohol  $\text{C}_{10}\text{H}_{21}\text{OH}$  is *n*-decyl alcohol. The general formula for each group of alcohols is easily written by recalling that a general formula for the series is  $\text{C}_n\text{H}_{2n+1}\text{OH}$ .

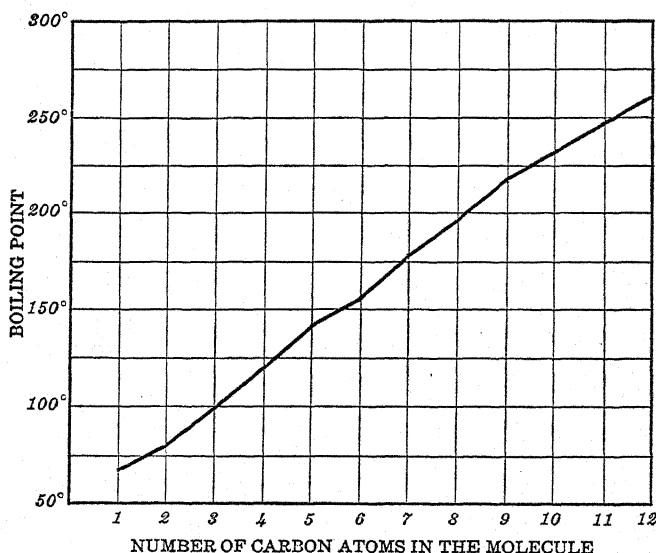
**Physical Properties of Alcohols.** If we compare the boiling points of the normal primary alcohols in the homologous series,

## 12 THE CHEMISTRY OF ORGANIC COMPOUNDS

a very interesting gradual and regular change is noticed. This is illustrated below:

PHYSICAL PROPERTIES OF NORMAL PRIMARY ALCOHOLS

NAME	FORMULA	BOILING POINT	DENSITY AT 25°	SOLUBILITY GRAMS PER 100 GRAMS OF WATER at 20°
Methyl alcohol	$\text{CH}_3\text{OH}$	65°	0.792	∞
Ethyl alcohol	$\text{CH}_3\text{CH}_2\text{OH}$	78°	0.785	
Propyl alcohol	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$	98°	0.799	
Butyl alcohol	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	118°	0.805	8.3
Amyl alcohol	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	138°	0.816	2.6
Hexyl alcohol	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	156°	0.820	less than 1

Fig. 1. The boiling points of normal primary alcohols from  $\text{CH}_3\text{OH}$  to  $\text{C}_{12}\text{H}_{25}\text{OH}$ .

The graph (Fig. 1) shows that for the *normal primary alcohols* there is a regular increase in boiling point with increasing number of carbon atoms. The higher members of the series are solids at room temperature. Thus *n*-decyl alcohol,  $\text{C}_{10}\text{H}_{21}\text{OH}$ ,

melts at 7°. The normal primary alcohol with the formula  $C_{32}H_{65}OH$  melts at 89°.

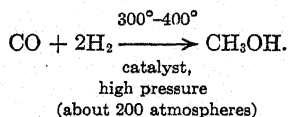
The isomeric alcohols differ in boiling point as illustrated by the table just below. In general, for a group of isomeric alcohols, branching the carbon chain lowers the boiling point but increases the solubility in water.

PHYSICAL PROPERTIES OF THE ISOMERIC BUTYL ALCOHOLS

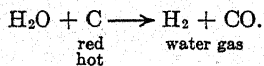
NAME	FORMULA	BOILING POINT	DENSITY AT 25°	SOLUBILITY GRAMS PER 100 GRAMS OF WATER AT 20°
<i>n</i> -Butyl Alcohol (Butanol)	$CH_3CH_2CH_2CH_2OH$	118°	0.805	8.3
Isobutyl Alcohol	$(CH_3)_2CHCH_2OH$	108°	0.804 (at 16°)	23
Secondary Butyl Alcohol	$CH_3CH_2$ $\quad \quad \quad \diagup \text{CHOH}$ $\quad \quad \quad CH_3$	100°	0.807	13
Tertiary Butyl Alcohol	$(CH_3)_3COH$	83°	0.780	completely soluble

## THE INDUSTRIAL PREPARATION OF IMPORTANT ALCOHOLS

**Methyl Alcohol (Methanol).** Methyl alcohol is prepared commercially on a very large scale by the interaction of carbon monoxide and hydrogen. The process can be represented by the following simple equation:



The mixture of hydrogen and carbon monoxide can be obtained very cheaply by the "water-gas reaction" which involves passing water vapor over hot coke:



The exact details of converting this mixture into methyl alcohol are somewhat complicated, but very high pressures and temperatures and a catalyst consisting of zinc and chromium oxides are the essential requirements (Fig. 2). Under the most favorable conditions the product is at least 99 per cent pure, the other material present being chiefly water.

This synthesis of methyl alcohol illustrates very well the importance to the organic chemist of a knowledge of the conditions which are necessary for a reaction to take place; such conditions are temperature, pressure, and presence of substances which act as catalysts. Raising the temperature  $10^{\circ}$  approximately doubles the rate of most reactions.

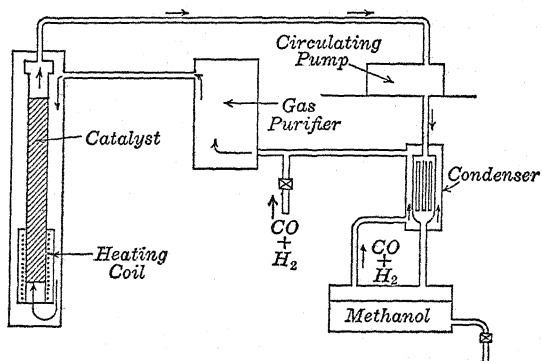


Fig. 2. Diagram illustrating the essentials of an apparatus for the synthesis of methyl alcohol from carbon monoxide and hydrogen.

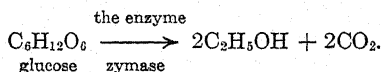
Many reactions proceed at an *appreciable rate* only under very definite conditions, and an equation representing only the formulas of the reactants and products has little meaning. In this book special conditions will be indicated over the arrow; when no temperature is indicated, it is assumed that the reaction proceeds at a convenient rate at room temperature or somewhat higher (*i.e.*,  $20^{\circ}$ – $80^{\circ}$ ).

Formerly the destructive distillation of wood was the only source of methyl alcohol. For this reason it was commonly called **wood alcohol**. The introduction of the synthetic method just described not only disturbed the wood distillation industry, but also lowered the price of methyl alcohol and caused a tremendous increase in consumption. Today nearly 90 per cent of the methanol consumed

is made by the synthetic method. The improvement of methods in the wood distillation industry, and the fact that an industrial and domestic demand for wood charcoal exists, makes it probable that synthetic methanol will not completely displace wood methanol from the market.

**Methyl Alcohol from Wood.** In the wood distillation process pre-dried wood is placed in a large iron retort and heated in the absence of air until all the volatile material is expelled. The residue is wood charcoal. The liquid distillate is a mixture containing about 1 per cent methyl alcohol, 5 to 8 per cent acetic acid (p. 86), and about 0.1 per cent acetone (p. 129) which can be separated by proper manipulations.

**Preparation of Ethyl Alcohol.** Ethyl alcohol has been prepared for centuries by **fermentation**. If a dilute solution of glucose (a sugar) is allowed to stand, it slowly changes into alcohol and carbon dioxide as represented by the following equation:

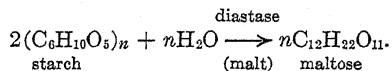


**The Cause of Fermentation.** The change of grape juice to wine is a very old example of fermentation. Thanks very largely to the labors of Pasteur,<sup>1</sup> it has been established that this change ordinarily takes place only if some living organism is present in the sugar solution or comes in contact with it. The usual organism is some variety of yeast. For a number of years after Pasteur's researches it was believed that the actual growth of the yeast or other organism was responsible for the change of the sugar into alcohol and carbon dioxide. Buchner<sup>2</sup> showed, however, that if one takes yeast and kills it by grinding with sand so that all the cells are completely destroyed and then squeezes the material through a very fine-pored filter, the resulting extract has the power of changing sugar into alcohol. This extract contains no living substance, but must contain very minute quantities of some remarkable catalyst formed by the yeast cell in its growth. This substance has been called **zymase**. It is an example of the class of natural catalysts known as **enzymes** (see p. 590).

<sup>1</sup> Louis Pasteur (1822-1895). Professor at the École Normale at Paris, 1857-1888; Director of the Pasteur Institute, 1885-1895.

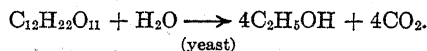
<sup>2</sup> Eduard Buchner (1860-1917). Professor of Organic Chemistry at the University of Würzburg.

**Alcohol from Starch.** The preparation of alcohol from starch illustrates the action of another enzyme. It is called **diastase**. It is formed when barley begins to sprout in a warm, damp atmosphere. This is the industrial source. In order to obtain this enzyme in quantity, barley is allowed to sprout and is then heated to a temperature which stops the sprouting but does not destroy the diastase. Barley thus treated is known as malt. When malt is mixed with grain or potatoes and water, the diastase acts on the starch according to the following equation:



*Note.* Empirical formulas are here used, as the structural formula of starch has not yet been determined. (See Chap. XVII.)

The dilute solution of the sugar **maltose**, thus formed, can be fermented by yeast. The yeast produces a mixture of enzymes which bring about this fermentation:



**Industrial Alcohol.** Industrial ethyl alcohol is prepared today in America very largely by the fermentation of the residues from the purification of cane sugar, which are known as molasses. These are fermented with yeast until a 6 to 10 per cent solution of alcohol is obtained which is then fractionally distilled yielding 95 per cent alcohol. Industrial alcohol can be made from potatoes, grain, or other starchy substances by first allowing malt to change the starch into sugar and then fermenting and distilling. Some industrial ethyl alcohol is also manufactured from a by-product of the petroleum industry (p. 67). If industrial ethyl alcohol becomes a substance which is used by the community in very large amounts (which might occur if the gasoline supply were exhausted), the production of alcohol from cheap forms of starch would become an enormous industry of the greatest importance.

**Uses of Methyl and Ethyl Alcohol.** At present, methyl and ethyl alcohol are used as the starting point for the manufacture of many other organic substances, since they are relatively cheap. They are also used widely as solvents, because they dissolve a great variety of substances which do not dissolve in water. The paint and varnish industry, for example, uses large quantities of

both alcohols. The perfume, flavoring, and pharmaceutical industries use ethyl alcohol for preparing solutions of perfumes, flavors, and drugs. Extract of vanilla is an alcoholic solution of the flavoring constituent of the vanilla bean. Tincture of iodine is an alcoholic solution of iodine. Indeed, the words **extract** and **tincture**, when thus used, almost invariably denote alcoholic solutions. Because of its poisonous effect on the human system, methyl alcohol cannot be used for such purposes. Methyl and ethyl alcohols are widely used in anti-freeze mixtures for automobiles.

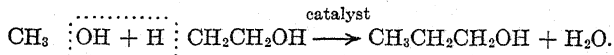
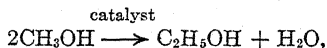
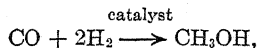
Ethyl alcohol is subject to a very heavy tax in all countries, and its sale is strictly regulated in the United States. If it is made unsuitable for drinking by the addition of methyl alcohol or other substances, it can be sold tax-free in most countries, including the United States. Such alcohol is said to be **denatured**. Methyl alcohol is the principal substance used for denaturing ethyl alcohol. In addition, certain amounts of evil-smelling substances are often included in order to afford a warning that the liquid is poisonous. The use of specially denatured alcohol with only slightly poisonous ingredients is allowed under government supervision in the manufacture of pharmaceutical preparations and in certain other industries.

It is possible that, in the future, denatured alcohol may be used as a fuel for internal combustion engines, but at present it is more expensive than gasoline. In relatively small quantities it is sold as a fuel for household use, in the form of **solid alcohol**. This is denatured alcohol containing a small amount of soap or nitrocellulose which causes the formation of a solid jelly.

**Absolute Alcohol.** Specially purified methyl and ethyl alcohols, free from water and other impurities, are known as absolute methyl alcohol and absolute ethyl alcohol. By careful distillation with a fractionating column, methyl alcohol can be obtained practically free from water. Strangely enough, the last 5 per cent of water cannot be removed from ethyl alcohol in this way. It can be removed by boiling the 95 per cent alcohol with calcium oxide. The calcium oxide combines with the water, forming calcium hydroxide, and the alcohol is left unchanged and can be finally distilled. This is the method commonly employed in the laboratory. Industrially, absolute ethyl alcohol is prepared by taking advantage of the rather peculiar fact that a mixture of benzene ( $C_6H_6$ ), water, and ethyl alcohol in the proportions 18.4 per cent alcohol, 74.1 per cent benzene, 7.4 per cent water, distils at a lower temperature than any one of the three pure substances. Benzene is added to the 95 per cent alcohol, and the mixture carefully distilled; the first fraction (b.p.  $65^\circ$ ) consists of alcohol,

water, and benzene. After all the water has been thus removed, the boiling point rises to about  $68^{\circ}$ , and the distillate is a mixture of alcohol and benzene; finally absolute alcohol distills at  $78.3^{\circ}$  C., and is collected. Absolute alcohol slowly absorbs water from the air, and must be kept carefully sealed in order to remain free from water.

**Industrial Uses of Higher Alcohols.** During the last twenty years the industrial production of some of the higher alcohols has been developed, and they have become substances of commercial importance. They are largely used as solvents either directly or in the form of their esters (compounds which are readily formed from the alcohols as will be described in Chap. V). They are also used as the starting point in the manufacture of a number of other organic compounds of industrial importance. The most important higher alcohol from the industrial standpoint is *n*-butyl alcohol (butanol),  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ , prepared from corn starch or by a series of reactions from acetylene (p. 147). Normal propyl alcohol,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ , has recently been manufactured from carbon monoxide and hydrogen by slight modifications of the catalyst used in the synthesis of methanol from the same materials (p. 13); other higher alcohols can also be produced in this way. The reaction probably proceeds in this manner:



Two secondary alcohols, isopropyl alcohol,  $\text{CH}_3\text{CHOHCH}_3$ , and secondary butyl alcohol,  $\text{CH}_3\text{CHOHCH}_2\text{CH}_3$ , and a tertiary alcohol, tertiary butyl alcohol,  $(\text{CH}_3)_3\text{COH}$ , as well as a number of the isomeric amyl alcohols,  $\text{C}_5\text{H}_{11}\text{OH}$ , are manufactured from petroleum and natural gas by processes which will be discussed later (Chap. IV). As yet none of them have attained the industrial importance of butanol.

Some normal alcohols of longer straight chains are now of industrial importance. Among these are lauryl alcohol,  $\text{C}_{12}\text{H}_{25}\text{OH}$ , cetyl alcohol,  $\text{C}_{16}\text{H}_{33}\text{OH}$ , and stearyl alcohol,  $\text{C}_{18}\text{H}_{37}\text{OH}$ . These alcohols are used as emulsifying agents, as bases for pharmaceuti-

cal preparations, and in making new detergents (p. 187). They are manufactured by methods to be described later.

**Butanol by the Fermentation Process.** The manufacture of the higher alcohols first started after the World War; before this time a mixture of several amyl alcohols known as fusel oil was the only commercial source of the higher alcohols. This fusel oil was a by-product of the preparation of ethyl alcohol by the fermentation of grains, and was therefore limited in amount and relatively an unimportant material. During the World War a process was developed for the production of acetone (p. 129) from corn starch by the use of a special bacillus which brought about the formation of carbon dioxide, gaseous hydrogen, acetone ( $C_3H_6O$ ), and *n*-butyl alcohol, — the last two substances appearing instead of the ethyl alcohol in the ordinary fermentation. The butyl alcohol was at first regarded as a worthless by-product while the desired material was acetone, which was required as a solvent in the manufacture of the smokeless powder used by the British. After the war, organic chemists turned their attention to finding a use for the butyl alcohol which had accumulated. It was soon discovered that the esters prepared from butyl alcohol were particularly suitable as solvents for the lacquers which were then being introduced into the automobile industry. The rapid expansion of the lacquer industry stimulated the manufacture of butyl alcohol, and the war time process was soon revived with the emphasis now reversed; butyl alcohol was the important product, acetone the by-product. Within the last few years even the carbon dioxide and hydrogen evolved in the fermentation have been used in preparing a solvent of value. Methyl alcohol is prepared by purifying the mixed gases and passing them over a suitable catalyst at high pressure. The carbon dioxide is first reduced to carbon monoxide, which then combines with the hydrogen to form methyl alcohol as explained in a preceding paragraph. The great commercial success of the production of *n*-butyl alcohol has undoubtedly stimulated the production of the other higher alcohols by a variety of processes.

**Chemical Properties of the Alcohols.** The characteristic grouping of the alcohols is the hydroxyl group. We have already seen in the case of ethyl alcohol that this group can react in two different ways (equations 1b and 2b, p. 6). The hydrogen atom attached to the oxygen may be replaced, as in the formation of sodium ethylate ( $C_2H_5ONa$ ), by the action of metallic sodium. This is a general reaction of alcohols; metallic potassium reacts in the same manner as sodium. The resulting compounds are obtained as colorless crystalline solids by boiling off the excess alcohol; they are known as the **alcoholates**. The student will readily recognize that in this reaction the alcohols somewhat resemble the inorganic acids, which are characterized by having a hydrogen replaceable by metals. However, the common metals such as zinc and iron which will react with acids are without effect

on alcohols; furthermore, alcohols in water solution are not neutralized by the bases; instead the compound  $\text{C}_2\text{H}_5\text{ONa}$  is completely hydrolyzed by water forming alcohol and sodium hydroxide:



For these reasons we do not usually regard alcohols as acids.

The interaction of phosphorus trichloride and ethyl alcohol illustrates a second type of reaction in which the whole *hydroxyl group* is replaced. We shall consider in the next chapter a number of reactions of the alcohols which lead to the production of many interesting and important substances. All these reactions fall into one of two classes, — either the hydrogen atom of the hydroxyl group is involved or the entire hydroxyl group is replaced by another atom or group. These replacement reactions are characteristic of all the compounds  $\text{C}_n\text{H}_{2n+1}\text{OH}$  irrespective of whether they are primary, secondary, or tertiary alcohols.

The lower members of the alcohol series resemble water, as might be expected from the presence of a hydroxyl group. With the increase of the number of carbon atoms in the molecule, the influence of the hydroxyl group becomes less pronounced and the similarity to water becomes less evident. This is clearly seen in the progressive decrease in the solubility in water of the alcohols above propyl. Another illustration of the same principle is seen in the fact that methyl and ethyl alcohol combine with a number of inorganic salts such as calcium chloride forming crystalline compounds containing *alcohol of crystallization*; for example,  $\text{CaCl}_2 \cdot 4\text{C}_2\text{H}_5\text{OH}$ ;  $\text{MgCl}_2 \cdot 6\text{CH}_3\text{OH}$ . The analogy between alcohol of crystallization and water of crystallization is evident. The higher alcohols do not combine with inorganic salts in this manner.

### QUESTIONS AND PROBLEMS

1. Define and illustrate the terms: homologous series, isomerism.
2. Describe briefly the industrial manufacture of ethyl alcohol from starch.
3. Present the evidence that shows that the alcoholic fermentation of sugar is caused by an enzyme present in the yeast cell.
4. Write balanced equations showing the industrial method of preparing methyl alcohol from coke.
5. Calculate the percentage composition of (a)  $\text{C}_2\text{H}_6$ , (b)  $\text{C}_4\text{H}_{10}\text{O}$ , (c)  $\text{C}_6\text{H}_7\text{N}$ , (d)  $\text{C}_6\text{H}_5\text{NCl}$ .
6. Calculate the empirical formulas of the substances which gave the following percentages of the elements on analysis: (a) C, 65.0; H, 13.5; (b) C,

60.0; H, 13.3: (c) C, 53.5; H, 15.5; N, 31.1: (d) C, 92.3; H, 7.7: (e) C, 9.40; H, 2.15; I, 89.40. (Hint: The percentage of oxygen is obtained by difference, the absence is assumed of elements other than those stated.)

7. If 1 liter of vapor of the substance in 6a weighs 2.42 g. at 100°, 760 mm., what is the molecular formula?

8. A gas has the following analysis: C, 52.2; H, 13.0. 1 liter at 0°, 760 mm. weighs 2.05 g.; what is the formula?

9. Write structural formulas for (a) all the butyl alcohols; (b) all the amyl alcohols; (c) all the straight chain hexyl alcohols. Arrange all these compounds into three groups according as to whether they are primary, secondary or tertiary alcohols.

10. Knowing that the boiling point of ethyl alcohol is 78°, predict the approximate boiling point of the normal primary alcohol,  $C_7H_{15}OH$ . Confirm your prediction by reference to Fig. 1. Would you expect a tertiary alcohol with the formula  $C_7H_{15}OH$  to boil higher or lower than this temperature?

11. Describe the laboratory method and the industrial method for preparing absolute ethyl alcohol. Why is not anhydrous calcium chloride used in drying ethyl alcohol?

12. In what respects do the alcohols resemble water?

13. Write the structural formula of potassium alcoholate. How is it prepared? In what ways do alcoholates differ from inorganic salts?

14. 1.76 gms. of an alcohol when treated with potassium gave off 448 cc. of hydrogen under standard conditions; what is the molecular weight of the alcohol?

15. Why is methyl alcohol used in automobile radiators to prevent freezing? Assuming the cost of amyl alcohol and methyl alcohol to be the same, which of the two would you choose for this purpose? Explain.

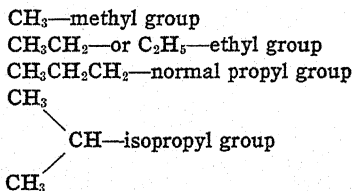
## CHAPTER II

### ALKYL HALIDES, ESTERS, ETHERS

In this chapter we shall continue a study of the alcohols by examining in more detail some of their general reactions and the substances which can be prepared from the alcohols by these reactions. We have already seen that a substance  $C_2H_5Cl$  is formed by the interaction of phosphorus trichloride and ethyl alcohol. It is a representative of one of the most important classes of organic compounds, — the *alkyl halides*. Since they are readily prepared from the alcohols and in turn can be transformed into many compounds, we shall find that they are of great value to the chemist.

#### ALKYL HALIDES

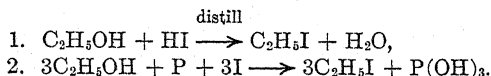
The alkyl halides are compounds in which the hydroxyl group of the alcohol has been replaced by a halogen atom. For example, methyl chloride,  $CH_3Cl$ , may be prepared from methyl alcohol,  $CH_3OH$ , or ethyl chloride,  $C_2H_5Cl$ , from ethyl alcohol,  $C_2H_5OH$ . The group of atoms  $CH_3-$  and  $C_2H_5-$  are known as *alkyl groups*. Alkyl groups correspond to the carbon and hydrogen residue attached to the  $OH$  group of the alcohol. "Free alkyls" such as methyl  $CH_3$  and ethyl  $C_2H_5-$  are extremely reactive, unstable compounds which can not be isolated. For this reason, the groups are for practical purposes merely abstractions which are *useful in naming organic compounds*. The following are the common alkyl groups:



We may write general formulas for alcohols and alkyl halides if

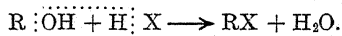
we let **R** represent any alkyl group. On this basis **ROH** is an alcohol and **RCI** an alkyl chloride.

**Preparation of Alkyl Halides.** Alkyl chlorides, bromides, and iodides are readily prepared by either of two methods. These may be illustrated by the equations for preparing ethyl iodide:



Both methods can be used with any simple alcohol. The second is commonly employed for preparing iodides; the iodine and phosphorus first react, forming phosphorus triiodide, this then reacts with the alcohol. Similarly, if one uses phosphorus tribromide or phosphorus trichloride instead of a mixture of phosphorus and iodine, the corresponding bromide and chloride can be prepared. Indeed, this is the reaction we first used to prove that ethyl alcohol contained an hydroxyl group.

**General Reactions.** The interaction of an alcohol and an acid may be written in a general form if we let **ROH** be any alcohol and **HX** be **HCl**, **HBr**, or **HI**:



Such a formulation expresses the fact that in general all alcohols can be transformed in the same manner to the corresponding halide. The conditions necessary for actually accomplishing such a transformation in a reasonable time, however, can not be generalized as they vary with the alcohol.

In this book we shall frequently write such *general reactions*. They are a convenient method of summing up our information about a reaction which we know proceeds with all members of an homologous series.

**Action of Halogen Acids on Alcohols.** Although the general reaction written above has a formal resemblance to the neutralization of an inorganic base by an acid, it is important to note that there is really very little analogy between the two cases. The inorganic reaction is instantaneous and takes place between ions. The product is a salt, a substance which is ionized in water solution. The preparation of the alkyl halide is slow, and in most cases only proceeds at a convenient rate either above room tem-

perature or in the presence of some catalyst such as zinc chloride. The product is not a salt but is an alkyl halide, a gas or liquid insoluble in water and not ionized.

**Variation in the Rates of a General Reaction.** It has been found by experience that most of the higher alcohols react faster with halogen acids than do methyl and ethyl alcohols. The speed of this reaction also varies with the type of alcohol. Thus, with halogen acids tertiary alcohols react more rapidly than do secondary, while primary alcohols are the least reactive. Tertiary butyl

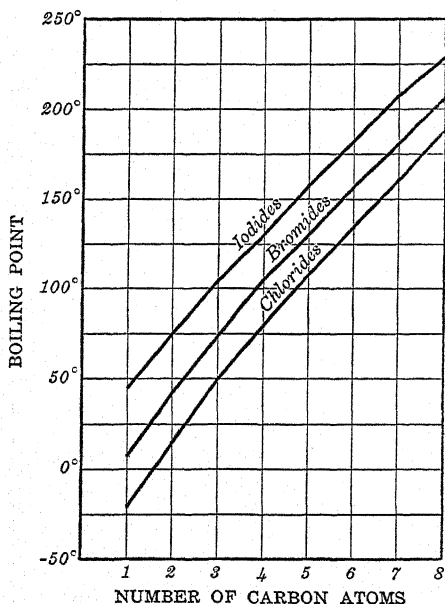


Fig. 3. The boiling points of the alkyl halides,  $\text{CH}_3\text{X}$  to  $\text{C}_6\text{H}_{13}\text{X}$ .

alcohol when mixed with concentrated hydrochloric acid at room temperature forms tertiary butyl chloride  $(\text{CH}_3)_3\text{CCl}$  almost instantaneously, while with normal butyl alcohol the reaction is slow and requires zinc chloride as a catalyst. In the case of those alcohols which are but very slightly soluble in water, aqueous acids can not be used. Instead the alcohol is saturated with the dry halogen acid gas. The speed of the reaction with primary alcohols is in the following decreasing order:  $\text{HI} > \text{HBr} > \text{HCl}$ .

Such variations in the speed of a general reaction in individual cases are the rule in organic chemistry. In this book we shall not emphasize such variations unless they are so great as to constitute a special case by themselves.

**Physical Properties.** The properties of certain of the alkyl halides are tabulated below and in the diagram (Fig. 3). It is convenient to remember that the simplest chloride which is a liquid at room temperature is the propyl compound, the simplest bromide the ethyl compound, and that methyl iodide is the only

methyl halide which is not a gas under ordinary conditions. The general effect on the boiling point of increasing the molecular weight is well illustrated by the properties of the alkyl halides. The alkyl halides are all practically insoluble in water and the bromides and iodides have a density greater than one.

## REPRESENTATIVE ALKYL HALIDES

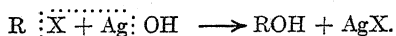
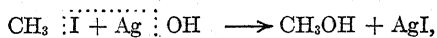
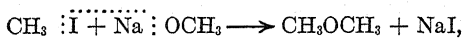
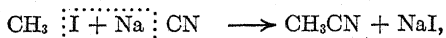
NAME	FORMULA	BOILING POINT	DENSITY AT 20°
<i>Chlorides</i>			
Methyl chloride	$\text{CH}_3\text{Cl}$	-24°	0.991 (at -24°)
Ethyl chloride	$\text{CH}_3\text{CH}_2\text{Cl}$	+12°	0.910
<i>n</i> -Propyl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$	47°	0.890
Isopropyl chloride	$\text{CH}_3\text{CH}(\text{Cl})\text{CH}_3$	37°	0.860
<i>Bromides</i>			
Methyl bromide	$\text{CH}_3\text{Br}$	+ 5°	1.732 (at 0°)
Ethyl bromide	$\text{CH}_3\text{CH}_2\text{Br}$	38°	1.430
<i>n</i> -Propyl bromide	$\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$	71°	1.353
Isopropyl bromide	$\text{CH}_3\text{CH}(\text{Br})\text{CH}_3$	60°	1.310
<i>Iodides</i>			
Methyl iodide	$\text{CH}_3\text{I}$	+43°	2.279
Ethyl iodide	$\text{CH}_3\text{CH}_2\text{I}$	72°	1.933
<i>n</i> -Propyl iodide	$\text{CH}_3\text{CH}_2\text{CH}_2\text{I}$	102°	1.747
Isopropyl iodide	$\text{CH}_3\text{CH}(\text{I})\text{CH}_3$	90°	1.703

**Industrial Uses.** Methyl and ethyl chlorides are the only alkyl halides commonly met. They are used in refrigerating machines on account of their low boiling points. The ethyl compound is used in the manufacture of lead tetraethyl (p. 29).

Ethyl chloride is employed as a local anesthetic in a rather peculiar way. It is sold as a liquid in small metal cylinders under pressure. When a stream of the liquid is directed on the surface skin, it boils on striking the warm body, thus abstracting heat from the skin. This process continues until the surface is frozen, so that the nerves no longer register pain when an incision is made.

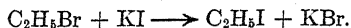
**Reactions of Alkyl Halides.** An important and characteristic reaction of an alkyl halide is one in which the halogen combines with a metallic atom and is thus replaced by another atom or

group. Several illustrations of this type of *metathetical reaction* are given below:



In all such metathetical reactions the iodides react most rapidly, the chlorides least rapidly, the bromides occupying an intermediate position.

Another metathetical reaction of alkyl halides is the replacement of one halogen atom by another. This is carried out by heating an alkyl halide with an inorganic halide in an anhydrous solvent (anhydrous acetone and lithium or potassium halides are often employed).

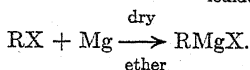
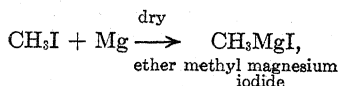


Alkyl iodides and bromides are generally used in the laboratory, but industrially the expense of iodine and bromine is so great that the chlorides are used in spite of the relative slowness with which they react. Like all other reactions, increasing the temperature greatly accelerates the metathetical reactions of the alkyl halides. In the laboratory it is usual to keep the temperature of the reaction mixture at the boiling point of the alkyl halide by having a return condenser attached to the vessel. The low boiling point of the simple alkyl halides thus prevents a large increase in temperature. In the industries, however, the reaction mixture can be placed in closed heavy metal cylinders, known as *autoclaves*; they are capable of withstanding high pressures. In such an apparatus the reaction temperature can be raised far above the boiling point of the alkyl halide, if necessary, in order to complete the reaction in a short time.

**Importance in Syntheses.** The alkyl halides are an important class of compounds because they enter into a large number of chemical reactions. They serve as a starting point for the preparation of a variety of other classes of organic compounds. We shall often have occasion to utilize the alkyl halides for this purpose.

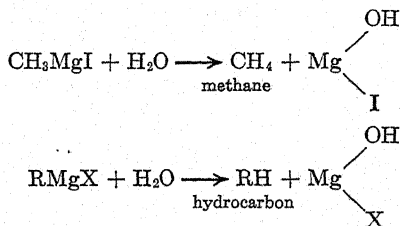
**The Grignard Reaction.** Another reaction of the alkyl halides of great importance in synthesis is the reaction with metallic magnesium. This reaction was discovered by the French chemist

Grignard.<sup>1</sup> In recognition of this discovery he was awarded one-half the Nobel Prize for the year 1912. The method of procedure is illustrated by Fig. 4; the equations are:



(In the general equations RX stands for any alkyl halide.)

In general, compounds of the type  $\text{RMgX}$  are called **Grignard reagents**; they are prepared and used in ether solution. They react with water violently at room temperature; this reaction enables us to prepare a type of substance known as a hydrocarbon which we are going to discuss in detail in the next chapter. The reaction between a Grignard reagent and water may be illustrated using methyl magnesium iodide:



In a similar manner methyl magnesium iodide will form methane when treated with acids, alcohols, ammonia, and many other

<sup>1</sup> Victor Grignard (1871-1935). Professor at the Chemical Institute of Lyons, France.

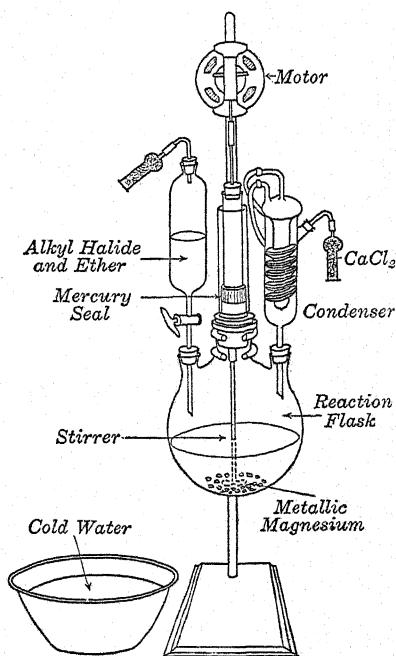
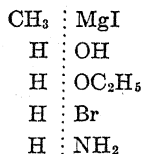


Fig. 4. A convenient laboratory apparatus for the preparation of methyl magnesium iodide or other Grignard reagents.

The magnesium turnings and dry ether are placed in the flask and the alkyl halide slowly added while the mixture is vigorously stirred. If necessary, the reaction is cooled by surrounding the flask with cold water.

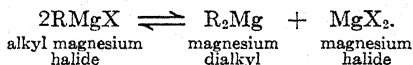
substances which have a so-called "active hydrogen." This is illustrated by the following diagram:



Since the product methane is a gas it can be conveniently collected and measured, and the amount of "active hydrogen" in a given weight of material may thus be estimated.

Other reactions of the Grignard reagent are used in the preparation of organic compounds; these will be discussed in a later chapter.

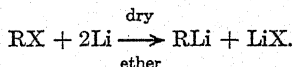
**Constitution of the Grignard Reagent.** Although the Grignard reagent is represented above as  $\text{RMgX}$ , considerable evidence has been gathered to indicate that it is an equilibrium mixture as illustrated below:



By adding dioxane (p. 177) to a Grignard reagent,  $\text{RMgX}$  and magnesium halide are precipitated leaving magnesium dialkyl in solution. The latter substance may also be obtained by distilling the Grignard reagent. Since, however, in most reactions the behavior of the Grignard reagent is best represented by  $\text{RMgX}$ , this formulation is always used.

**Other Metallic Alkyls.** A large number of organometallic compounds which are prepared directly or indirectly from alkyl halides are known. Of these we shall mention a few.

**Lithium alkyls** can be prepared from alkyl halides and lithium in the presence of ether.

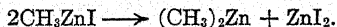


They have found use in instances where magnesium reacts very sluggishly with the alkyl halide. In general, lithium alkyls behave as the Grignard reagent in chemical reactions.

**Zinc alkyls** can be made from alkyl halides and zinc coated with copper, in the presence of a small quantity of ethyl acetate.

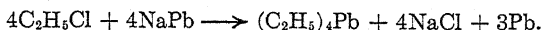


For the most part they are similar to the Grignard reagent in their reactions, and are used only for a few special reactions. Like the Grignard reagent, zinc alkyls on distillation give a metallic dialkyl,  $\text{ZnR}_2$ ,



The zinc alkyls are spontaneously inflammable in air, and the preparation must therefore be carried out in an inert gas such as hydrogen or nitrogen. They were first prepared by Frankland<sup>1</sup> and before the discovery of the Grignard reagent the zinc alkyls were frequently used in the preparation of organic substances in the laboratory. Now they are almost entirely displaced by the Grignard reagent.

Lead tetraethyl produced commercially in large amounts (about 10 thousand tons annually) for the gasoline industry (p. 55) is prepared from ethyl chloride and one of the alloys of lead and sodium.

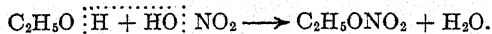


It is a highly toxic liquid soluble in organic solvents and boils at 202° C.

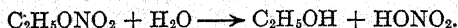
**Alkyl Fluorides.** Just as the element fluorine differs considerably from the other members of the halogen family, so the alkyl fluorides are compounds which have but little in common with the alkyl chlorides, bromides, and iodides. They are usually prepared by a special reaction — the interaction of an inorganic fluoride and an alkyl halide — though they may be formed by heating an alcohol with hydrofluoric acid. The lower alkyl fluorides are all gases; propyl fluoride boils at -2°, *n*-amyl fluoride at 63°. Unlike the chlorides, bromides, and iodides the halogen atom in the fluorides is very unreactive. Methyl fluoride reacts but very slowly with even strong sodium hydroxide or sodium ethylate.

#### ESTERS OF INORGANIC ACIDS

**Esterification.** When an alcohol and an acid are brought together, the hydroxyl group of the acid and the hydrogen of the alcohol unite to form water; a new compound is formed which is an ester. The reaction is known as **esterification**. It takes place very rapidly at room temperature with nitric or sulfuric acid, and, unless carefully controlled, may be explosive with the former substance. The equation for the formation of ethyl nitrate from nitric acid and ethyl alcohol is as follows:



**Alkyl Nitrates.** Ethyl nitrate,  $\text{C}_2\text{H}_5\text{ONO}_2$ , is a liquid with a pleasant odor, heavier than water: it boils at 89°. When boiled with water, it is hydrolyzed forming ethyl alcohol and nitric acid. This hydrolysis reaction is a general property of esters; the reaction is:



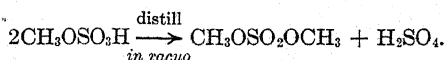
<sup>1</sup> Edward Frankland (1825-1899). An English chemist whose work laid the foundations of the theory of valence.

**Alkyl Nitrites.** The esters of the unstable nitrous acid are known as nitrites. They are prepared by distilling a mixture of the alcohol, sodium nitrite ( $\text{NaNO}_2$ ), and sulfuric acid. **Ethyl nitrite**,  $\text{C}_2\text{H}_5\text{ONO}$  (boiling at  $17^\circ$ ), is sold in an alcoholic solution as "sweet spirits of nitre." **n-Butyl nitrite** is a pale yellow liquid which boils at  $75^\circ$ ; **amyl nitrite** boils at  $99^\circ$ . Both these nitrites are used in the laboratory as sources of nitrous acid. Amyl nitrite like ethyl nitrite is used in medicine.

**Esters of Sulfuric Acid.** Since sulfuric acid is an acid with two hydrogen atoms, it can form two types of esters just as it can form two classes of salts. **Ethyl sulfuric acid**,  $\text{C}_2\text{H}_5\text{OSO}_3\text{H}$ , is both an ester and an acid. **Diethyl sulfate**,  $\text{C}_2\text{H}_5\text{OSO}_2\text{OC}_2\text{H}_5$ , and **dimethyl sulfate**,  $\text{CH}_3\text{OSO}_2\text{OCH}_3$ , are examples of neutral esters of sulfuric acid.

Ethyl sulfuric acid (or ethyl hydrogen sulfate) is an oily liquid. It is usually prepared as needed by mixing sulfuric acid and alcohol; the reaction mixture contains water, some unchanged alcohol and sulfuric acid, and the desired ethyl sulfuric acid. Since the substance is both an acid and an ester, it has the characteristic properties of both classes. It forms salts when cautiously treated with bases and is hydrolyzed to alcohol and sulfuric acid when heated with water.

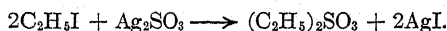
Dimethyl sulfate is prepared by heating methyl sulfuric acid,  $\text{CH}_3\text{OSO}_3\text{H}$ , under *diminished pressure*. The equations for the steps in its preparation are as follows:



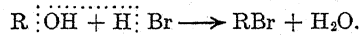
Dimethyl sulfate is a heavy liquid, boiling at  $188^\circ$ , very poisonous and practically without odor. It is used in place of methyl iodide in certain reactions in which the methyl group is to be introduced into an organic molecule (p. 35). It is much cheaper than the iodide and therefore is quite generally employed for such purposes in industrial processes.

**Preparation of Esters from Inorganic Salts.** Esters may also be prepared by the action of alkyl halides (preferably the iodides) on the silver salts of acids. In this way the esters of certain unstable acids like sulfurous acid can be formed which would be

otherwise unknown. The following equation illustrates the preparation of diethyl sulfite,  $C_2H_5OSOOC_2H_5$ :



**Alkyl Halides as Esters.** The alkyl halides may be regarded as the esters of the halogen acids. The first of the two methods of preparation which have already been given (p. 23) is an esterification reaction as the following equation shows:



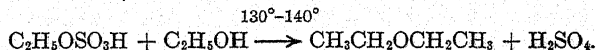
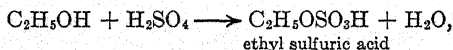
On boiling with water, many alkyl halides are slowly converted into the alcohol and the halogen acid; thus the typical hydrolysis reaction of esters is also a property of the alkyl halides.

The separation of the esters of the three halogen acids into one separate class is merely a matter of convenience. These esters of the halogen acids enter into many reactions (such as the formation of the Grignard reagent) which can not be brought about with other esters. For this reason it is best, in an elementary survey of organic chemistry, to distinguish the alkyl halides from the esters of other acids. The esters of organic acids are considered in Chapter V. The esters of certain of these acids form a large class of natural substances known as the fats and oils.

## ETHERS

Another important class of substances which are prepared directly from the alcohols are the ethers. The nature of these compounds will be best understood by studying the commonest representative, diethyl ether, usually called simply ether. It has been an important substance for nearly a hundred years; without this anesthetic modern surgery might never have developed.

**Preparation of Ethyl Ether.** Ether is readily prepared from ethyl alcohol by heating this substance with sulfuric acid. The following reactions take place:



The preparation of ether from alcohol by this method is one of the oldest known organic reactions and is still the commercial process. Ether was manufactured in this way long before the nature of the reaction had been discovered. The alcohol is allowed to flow into a mixture of alcohol and sulfuric acid heated to  $130^{\circ}$ – $140^{\circ}$ ; ether and some alcohol and water distill and are condensed. The equations written above show that there are really two steps in the process: in the first, ethyl sulfuric acid is formed by interaction of ethyl alcohol and sulfuric acid; in the second, this substance reacts with more alcohol forming ether and regenerating sulfuric acid. The regenerated acid then reacts with more alcohol forming ethyl sulfuric acid (first reaction). At first sight it would appear that a given amount of sulfuric acid could thus keep on converting an unlimited amount of alcohol into ether. Actually this is not the case in the laboratory because as the sulfuric acid becomes more dilute, water and alcohol distill with the ether and the process becomes too inefficient.

The temperature of the reaction mixture must be controlled rather carefully. At temperatures below  $130^{\circ}$ , the second reaction is so slow that unchanged alcohol will distill; at high temperatures ( $150^{\circ}$ – $200^{\circ}$ ), ethyl sulfuric acid decomposes (p. 60). This is an excellent illustration of the principle mentioned in the last chapter, — namely, that the *conditions are of supreme importance in determining the course of an organic reaction*. In this case, a relatively slight change in the temperature greatly alters the efficiency of the process.

**Industrial Apparatus for Preparing Ether.** The industrial preparation of ether is illustrated by the diagram shown in Fig. 5. This is a simplified representation of the modern equipment which permits the production of an almost unlimited amount of ether from one charge of acid. The operation is as follows. The ether pot is charged with pure concentrated sulfuric acid; ethyl alcohol is then added and the mixture allowed to stand for some time during which ethyl sulfuric acid is formed (reaction 1, p. 31). The pot is then heated by passing steam through the coils which are below the level of the liquid. The temperature is kept at  $130^{\circ}$ , and alcohol is slowly run in from the alcohol feed-tank. The vapor which issues from the ether pot contains alcohol, water, ether, and a small amount of acid fumes (sulfur dioxide). The latter are removed by coming in contact with sodium hydroxide in the caustic scrubber. The vapors then pass through a series of complicated fractionating columns and partial condensers which separate the ether from the alcohol and water. The water and alcohol are separated in another column, and 95 per cent alcohol recovered. The temperatures of the ether pot and the various

fractionating columns are carefully regulated. The process may be run continuously for many weeks. Because of the fractionating columns which separate the ether, alcohol, and water the process is continuously efficient and, unlike the laboratory procedure, does not require recharging with sulfuric acid after considerable water has been formed. Even if the percentage of ether is low in the vapors as they leave the reaction, this ether is continuously separated by the columns and the unchanged alcohol is returned to be once again introduced into the reaction.

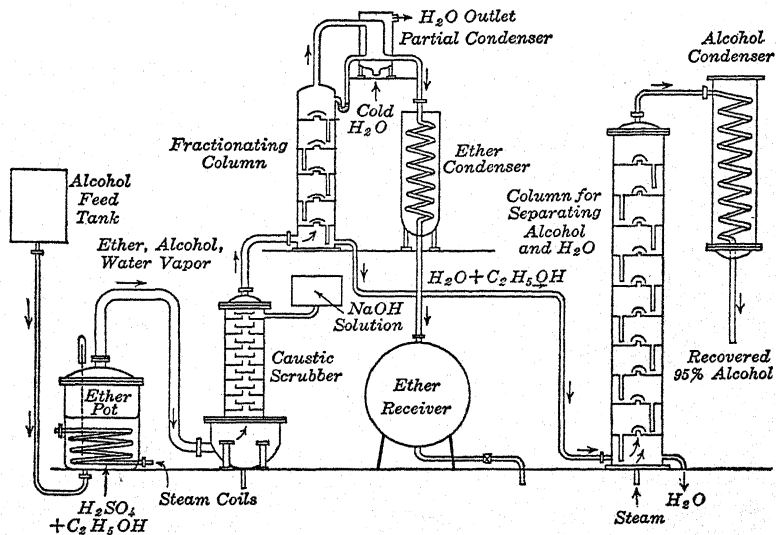


Fig. 5. Diagram of the essential parts of the apparatus used in the industrial preparation of ether. From data kindly furnished by E. B. Badger and Sons Co.

**Uses of Ethyl Ether.** Ether is a colorless liquid boiling at  $35^\circ$ . It has a rather pleasant odor. Ether is highly inflammable, and on standing, it slowly absorbs oxygen from the air to form unstable peroxides of unknown structure. In addition to its wide use as an anesthetic, it is a valuable solvent. Unlike alcohol, it is nearly insoluble in water and is lighter than water, and is therefore a favorite solvent for extracting substances from water solution. This is accomplished by shaking the water solution with ether. For example, if a solution of bromine in water is shaken with ether, the top ether layer will be colored red by the extracted bromine, and the aqueous layer will be colorless. The two layers are easily separated mechanically. Since ether has a low boiling point, it is usually an easy matter to distill it and leave the desired substance

behind. Salts, mineral acids, and bases do not pass into an ether layer under such a treatment, but almost all organic substances, except salts and polyhydroxy compounds, are extracted to some extent. By repeating the process, many times if necessary, the

organic material can be obtained in the ether layer. Figure 6 shows a laboratory apparatus which automatically accomplishes a repeated extraction of an aqueous solution. This is known as an apparatus for **continuous extraction**. The process of extraction with ether is much used in the laboratory and in industry for the separation of organic from inorganic material.

Ether is often used as a solvent in which the two substances are allowed to interact. Frequently for such purposes the ether must be free from water and alcohol as in the preparation of Grignard reagents. Such **absolute ether** is made by treating ordinary ether with anhydrous calcium chloride, and then distilling from metallic sodium or phosphorus pentoxide.

#### Homologous Series of Ethers.

The **homologous** series of ethers starts with methyl ether, the gas which is isomeric with ethyl alcohol; the first four members are given below. The lower members of this series are prepared

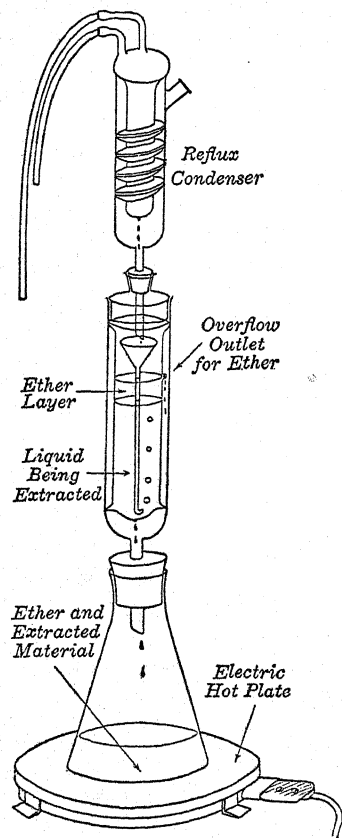
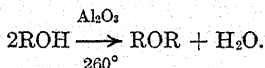


Fig. 6. Apparatus for the continuous extraction with ether of a small amount of an aqueous solution.

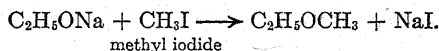
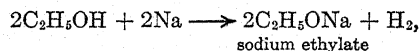
either by the interaction of sulfuric acid and the alcohol in question at an elevated temperature or by passing the vapors of a primary alcohol through a tube heated to  $260^{\circ}$  and containing alumina ( $\text{Al}_2\text{O}_3$ ):



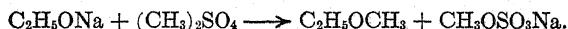
## HOMOLOGOUS SERIES OF ETHERS

NAME	FORMULA	BOILING POINT	DENSITY AT 20°	SOLUBILITY GRAMS PER 100 GRAMS OF WATER
Methyl ether	$\text{CH}_3\text{OCH}_3$	- 25°	—	1 vol. of water dissolves 37 vols. of gas
Ethyl ether	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	+ 35°	0.714	7.0
Propyl ether	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$	+ 91°	0.746 (at 19°)	6.0
Butyl ether	$(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{O}$	+143°	0.768	—

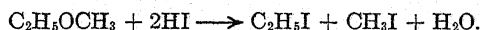
**Mixed Ethers.** Ethers with two different groups are called mixed ethers. Such an ether is methyl ethyl ether. It can not be prepared conveniently by the usual reaction, but instead is prepared by the Williamson<sup>1</sup> synthesis. The equations are as follows:



Instead of methyl iodide, dimethyl sulfate may be used:



**Chemical Reactions of Ethers.** Chemically, the ethers are noted for their inertness; they do not react with such reagents as metallic sodium, phosphorus trichloride, or alkalis. They are broken down into two molecules by warming with sulfuric acid or, more rapidly, with aqueous hydrogen iodide, as the following reaction shows:



This reaction is often used in determining the structure of ethers.

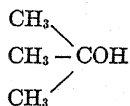
**Ethers of Industrial Importance.** Dimethyl ether is manufactured today by the catalytic dehydration of methanol. It finds use as a refrigerant since it can be allowed to come in direct contact with foodstuffs during "quick freezing" without imparting any foreign taste or odor. Isopropyl ether,  $(\text{CH}_3)_2\text{CHOCH}(\text{CH}_3)_2$ , (b.p. 69°) is commercially available, and in many industrial extraction processes it is beginning to replace ethyl ether. It is

<sup>1</sup> First used by A. W. Williamson (1824-1904). Professor at University College, London.

actually cheaper than ether, and because of its lower volatility it is less hazardous to handle. Higher ethers such as those obtained from the amyl alcohols are now produced. Their chief use is as solvents.

### A METHOD OF NAMING ALCOHOLS

The usefulness of the idea of alkyl groups is illustrated by the method commonly employed in naming those alcohols which are higher members of the methyl alcohol series. Such alcohols are named as derivatives of methyl alcohol,  $\text{CH}_3\text{OH}$ , which is called **carbinol** *when it is thus considered as a parent substance*. We then name the alkyl groups which are attached to the carbon atom which holds the OH group. Such alkyl groups are *substituents* since they may be regarded as having been substituted in place of a hydrogen atom of the parent substance. **Trimethyl-carbinol** is:



this is also written as  $(\text{CH}_3)_3\text{COH}$ .

**Methyl-ethyl-carbinol** is:  $\text{CH}_3\text{CHOHCH}_2\text{CH}_3$ .

**Methyl-isopropyl-carbinol** is:  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH} \\ | \\ \text{CH}_3 \end{array} \text{CHOHCH}_3$ ,

This is also written as  $(\text{CH}_3)_2\text{CHCHOHCH}_3$ .

For the sake of clarity, where there are a number of different alkyl groups hyphens are often used to separate the prefixes. It is equally correct to write an unhyphenated word, for example, methylisopropylcarbinol; it is usually considered *incorrect*, however, to write methyl isopropyl carbinol. In this book we shall use hyphens whenever there are prefixes representing several substituents. It is to be noted, however, that in the case of ethers where a general class name is used the nomenclature does not involve the idea of a substituent, and the alkyl groups are written separately, thus: methyl ethyl ether.

A convenient tabulation of the types of compounds we have so far considered in this book is given below:

NAME	GENERAL FORMULA	SPECIFIC EXAMPLE
Alcohol	ROH	CH <sub>3</sub> OH methyl alcohol
Ether	ROR	C <sub>2</sub> H <sub>5</sub> OC <sub>2</sub> H <sub>5</sub> ethyl ether
Mixed ether	ROR'	C <sub>2</sub> H <sub>5</sub> OCH <sub>3</sub> methyl ethyl ether
Alkyl iodide	RI	CH <sub>3</sub> I methyl iodide
Alkyl bromide	RBr	C <sub>2</sub> H <sub>5</sub> Br ethyl bromide
Alkyl chloride	RCI	C <sub>2</sub> H <sub>5</sub> Cl ethyl chloride
Alkyl halide in general	RX	see above
Esters		
Alkyl nitrate	RONO <sub>2</sub>	C <sub>2</sub> H <sub>5</sub> ONO <sub>2</sub> ethyl nitrate
Alkyl sulfuric acid	ROSO <sub>3</sub> H	C <sub>2</sub> H <sub>5</sub> OSO <sub>3</sub> H ethyl sulfuric acid
Alkyl sulfates	ROSO <sub>2</sub> OR	CH <sub>3</sub> OSO <sub>2</sub> OCH <sub>3</sub> dimethyl sulfate

## QUESTIONS AND PROBLEMS

1. Write structural formulas for: (a) *n*-butyl ether; (b) methyl isopropyl ether; (c) triethyl-carbinol; (d) dimethyl-isopropyl-carbinol; (e) diethyl-propyl-carbinol.

2. Name the following: (a) CH<sub>3</sub>CHOHCH<sub>2</sub>CH<sub>3</sub>; (b) (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>CHOH; (c) (CH<sub>3</sub>)<sub>2</sub>COHCH(CH<sub>3</sub>)<sub>2</sub>; (d) CH<sub>3</sub>OCH(CH<sub>3</sub>)<sub>2</sub>; (e) (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>OH; (f) CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>ONO; (g) (CH<sub>3</sub>)<sub>2</sub>CHONO<sub>2</sub>; (h) CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br; (i) CH<sub>3</sub>CH<sub>2</sub>CHICH<sub>3</sub>.

3. Write balanced equations showing: (a) the reactions used in the commercial preparation of ether; (b) two methods of preparing ethyl iodide; (c) preparation of methyl ethyl ether; (d) how you could distinguish between CH<sub>3</sub>CH<sub>2</sub>OH and CH<sub>3</sub>OCH<sub>3</sub>.

4. Write structural formulas for: isopropyl iodide; *n*-butyl bromide; tertiary butyl chloride; propyl chloride; *n*-butyl sulfuric acid.

5. How can one prepare *n*-amyl alcohol from *n*-amyl iodide? *n*-butyl alcohol from *n*-butyl nitrate? Write equations.

6. What is the Grignard reaction? Illustrate.

7. In what respects are the esters of nitric acid similar to the alkyl halides; in what respects different?

8. Why is methyl iodide more commonly employed in the laboratory than methyl bromide?

9. Write a balanced equation for the following reactions: (a) propyl-ethyl-carbinol and phosphorus tribromide; (b) ethyl magnesium bromide and ethyl alcohol; (c) isobutyl bromide and moist silver oxide; (d) *n*-amyl iodide and sodium methylate; (e) sodium ethylate and dimethyl sulfate.

10. By the use of Williamson's synthesis, how much ethyl and methyl alcohol are necessary to prepare 50 gms. of ethyl methyl ether, assuming an

## 38 THE CHEMISTRY OF ORGANIC COMPOUNDS

80 per cent yield in each step? (Consider the reaction of sodium and an alcohol to be quantitative.)

11. List the typical reactions of alkyl halides, and point out the significance of each.

12. Why is it necessary to use absolute ether in preparing the Grignard reagent? Starting with the crude product obtained from the laboratory method of preparing ether, how would you proceed to make absolute ether?

13. Write the structures of all the isomeric chloro compounds which have the empirical formula  $C_4H_9Cl$ .

## CHAPTER III

### SATURATED HYDROCARBONS. PETROLEUM

It is unnecessary to emphasize the importance of petroleum. Every one realizes to what extent the world is dependent on it as the source of that magical fluid, gasoline, which has made possible the automobile. To meet the ever-increasing demand, an enormous number of wells have been drilled and the search for the precious liquid has spread to all quarters of the globe. Although this is common knowledge, relatively few people understand

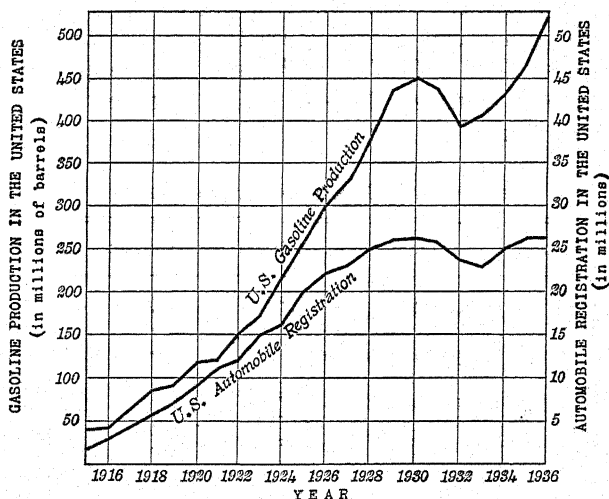


Fig. 7. Chart showing the increase in the annual gasoline production in the United States and the increase in automobile registration.

Gasoline production in millions of barrels each holding 42 gallons; automobile registration in millions.

that in the production of gasoline from petroleum there is a chemical problem, still only partially solved. The amount of gasoline which can be obtained from petroleum has been greatly increased in recent years by a chemical transformation of the high-boiling portions of the crude oil (essentially kerosene) into gasoline. A considerable portion of the gasoline supply today is

"manufactured" in this way, and this has enabled the oil industry to keep pace with the production of automobiles (Fig. 7). If a still higher yield of gasoline could be obtained, the exhaustion of the crude oil supply would be further postponed. To understand the problems of the manufacture and use of automobile fuels, we must study those substances, — the hydrocarbons — which constitute more than 90 per cent of crude petroleum.

**Petroleum, a Mixture of Hydrocarbons.** Both petroleum and gasoline are complex mixtures, and one can not define them accurately in chemical terms. It has been possible to isolate comparatively few pure substances from petroleum. These are **hydrocarbons**, — *substances composed solely of carbon and hydrogen*. They may be classified according to the *relative* number of carbon and hydrogen atoms. Thus, we have a series in which the number of hydrogen atoms is two more than twice the number of carbon atoms: thus,  $\text{CH}_4$ ,  $\text{C}_2\text{H}_6$ ,  $\text{C}_3\text{H}_8$ , etc.; this may be expressed by the general formula,  $\text{C}_n\text{H}_{2n+2}$ . This is called the **paraffin**, **methane**, or **alkane** series.

SOME NORMAL PARAFFIN HYDROCARBONS

MOLECULAR FORMULA	NAME	BOILING POINT	MELTING POINT	DENSITY AT 20°
$\text{CH}_4$	Methane	-161°	-184°	—
$\text{C}_2\text{H}_6$	Ethane	- 88°	—	—
$\text{C}_3\text{H}_8$	Propane	- 45°	—	—
$\text{C}_4\text{H}_{10}$	<i>n</i> -Butane	+ 0.6°	—	0.601 at 0°
$\text{C}_5\text{H}_{12}$	<i>n</i> -Pentane	36°	-148°	0.631
$\text{C}_6\text{H}_{14}$	<i>n</i> -Hexane	69°	- 94°	0.658
$\text{C}_7\text{H}_{16}$	<i>n</i> -Heptane	98°	—	0.683
$\text{C}_8\text{H}_{18}$	<i>n</i> -Octane	126°	- 98°	0.702
$\text{C}_9\text{H}_{20}$	<i>n</i> -Nonane	150°	- 51°	0.719
$\text{C}_{10}\text{H}_{22}$	Decane	174°	- 32°	0.747
$\text{C}_{11}\text{H}_{24}$	Undecane	194.5°	- 26.5°	0.758
$\text{C}_{12}\text{H}_{26}$	Dodecane	214-216°	- 12°	0.768
$\text{C}_{13}\text{H}_{28}$	Tridecane	234°	- 6.2°	0.757
$\text{C}_{14}\text{H}_{30}$	Tetradecane	252.5°	5.5°	0.774 at mp.
$\text{C}_{15}\text{H}_{32}$	Pentadecane	270.5°	10°	0.776 " "
$\text{C}_{16}\text{H}_{34}$	Hexadecane	287.5°	18°	0.775 " "
$\text{C}_{17}\text{H}_{36}$	Heptadecane	303°	22.5°	0.777 " "
$\text{C}_{18}\text{H}_{38}$	Octadecane	317°	28°	0.777 " "
$\text{C}_{19}\text{H}_{40}$	Nonadecane	330°	32°	0.777 " "
$\text{C}_{20}\text{H}_{42}$	Eicosan	205° (at 15 mm.)	36.7°	0.778 " "

Pennsylvania petroleum seems to be largely composed of hydrocarbons of this series, and the name paraffin is applied to the waxlike solid obtained as a residue from this oil by distillation. Natural gas contains the more volatile members of this series.

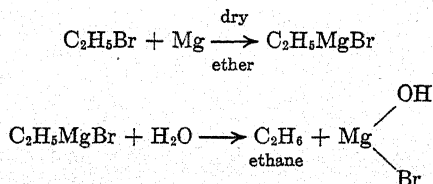
Since petroleum is such a complicated mixture of a variety of hydrocarbons, a detailed consideration of it is out of the question in an elementary course. Indeed, the experimental difficulty of separating pure compounds from gasoline or crude oil has been so great that there is still uncertainty on many fundamental chemical points. A knowledge of the chemistry of the various types of hydrocarbons is obviously the first step in the understanding of petroleum products. Fortunately, this can be fairly readily attained in the laboratory since there are many varied methods of preparing pure representative hydrocarbons.

Some of the fields yield petroleums which are composed of compounds containing less hydrogen than the methane series; they are the naphthene or cycloparaffin hydrocarbons (Chap. XXVI) and have the general formula of  $C_nH_{2n}$ . These hydrocarbons also occur in considerable amounts in the less-volatile fractions of Pennsylvania petroleum.

Still other types of hydrocarbons are represented by the ethylene series (also  $C_nH_{2n}$ ) and the aromatic series  $C_nH_{2n-6}$ ; members of these series occur to some extent in crude petroleum and are frequently found in connection with its chemical transformations; they will be considered in Chaps. IV and XVIII.

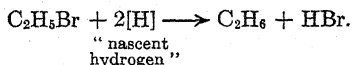
#### PARAFFIN OR ALKANE HYDROCARBONS

**Preparation.** Pure members of the paraffin series are most conveniently obtained by the action of water on the Grignard reagent. This reaction was described in the last chapter; another example is given below:



It will be noted that this method of preparing ethane amounts

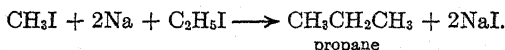
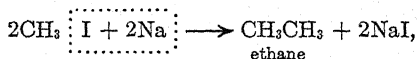
to the replacement of a bromine atom by an atom of hydrogen; it may be regarded as an indirect reduction brought about in two steps. Alkyl halides may also be converted into the corresponding hydrocarbon by direct reduction with "nascent hydrogen" generated by such combinations as zinc and acid, sodium and alcohol, or sodium amalgam and water.



The higher alkyl iodides may be reduced to hydrocarbons by heating with hydrogen iodide:

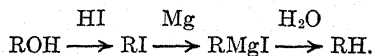


Higher members of the series may be prepared by joining two alkyl groups by the Wurtz<sup>1</sup> reaction in which metallic sodium reacts with an alkyl halide (or a mixture of two halides).



If two different alkyl halides are employed there will be always two products besides the desired hydrocarbon. Thus in the example just given, some ethane,  $\text{CH}_3\text{CH}_3$ , and some butane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$ , will also be formed. Unless the three products boil quite far apart it is very difficult to separate such a mixture. This fact limits the use of the Wurtz reaction.

**Derivatives of Hydrocarbons.** In the methods illustrated above, we have prepared hydrocarbons by employing alkyl halides which, in turn, can be prepared from the alcohols. An inspection of the formulas for methyl alcohol and methane shows that the latter may be regarded as formed by the replacement of the hydroxyl group by hydrogen. Although this can not be accomplished directly, it can be done indirectly through the alkyl halide and the Grignard reaction, as shown below.<sup>2</sup>



<sup>1</sup> Adolph Wurtz (1817-1884). Professor at the École de Médecine, Paris.

<sup>2</sup> In writing a series of chemical reactions which are involved in the synthesis of one compound from another it is often convenient to indicate the important reagent over the arrow. These are not equations and, therefore, are not balanced.

The relationship between the alcohols we have studied and the corresponding paraffin hydrocarbons is illustrated below:

ALCOHOL	ALKYL IODIDE	HYDROCARBON	NAME OF HYDROCARBON
$C_nH_{2n+1}OH$ ROH	$C_nH_{2n+1}I$ RI	$C_nH_{2n+2}$ RH	
CH <sub>3</sub> OH CH <sub>3</sub> CH <sub>2</sub> OH CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH CH <sub>3</sub> CHOHCH <sub>3</sub>	CH <sub>3</sub> I CH <sub>3</sub> CH <sub>2</sub> I CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> I CH <sub>3</sub> CHICH <sub>3</sub>	CH <sub>4</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>	methane ethane propane

The alcohols and alkyl halides are often spoken of as derivatives of the paraffin hydrocarbons. A derivative of a hydrocarbon is a substance which *might* be prepared from the hydrocarbon by the replacement of a hydrogen atom by a group or an atom. This is a purely formal relationship which is useful in classification. It does not state that the derivatives of the hydrocarbon are prepared in this way. Indeed, we shall see that they almost never are!

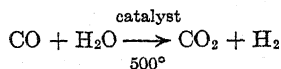
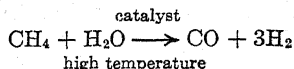
**Methane.** The first member of the paraffin series of hydrocarbons deserves a few words of special comment. Since it contains only one carbon atom it may be regarded as the simplest organic compound (the oxides of carbon and carbon itself are usually regarded as being outside the field of organic chemistry). Unless hydrogen has a valence greater than one, there can be no question of the structure of methane; its very existence demonstrates that carbon has a valence of four.

There are two special methods of preparing methane which are not applicable to the higher members of the series. These are:

1.  $CO + 3H_2 \xrightarrow{Ni\ catalyst} CH_4 + H_2O$
2.  $Al_4C_3 + 12H_2O \longrightarrow 3CH_4 + 4Al(OH)_3$

Methane is formed by the anaerobic fermentation of vegetable matter, a condition prevalent in the marshes. Since the gas which results from this process is largely methane, the latter is often called *marsh gas*. Methane is also present in large amounts in the hazardous gas known to the miners as *fire damp*. Natural gas and manufactured illuminating gas contain a high per-

centage of methane. A large industrial use for methane is in the production of commercial hydrogen. In this process steam and methane are heated to 800°–1000° C. in the presence of special catalysts. The products are hydrogen and carbon monoxide. The latter can react further with steam at 500° C. using a different catalyst to give carbon dioxide and hydrogen. Thus, four molecules of hydrogen are obtained from one of methane



**Isomerism in the Paraffin Series.** It will be noticed that only one substance, propane, corresponds to both propyl and isopropyl alcohols. Isomerism in the series of the paraffin hydrocarbons is not met with until we come to the butanes,  $\text{C}_4\text{H}_{10}$ . There are two of these, *n*-butane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$ , and isobutane,  $\text{CH}_3$   
 $\text{CH}_3$ —CHCH<sub>3</sub>; they boil at +0.6° and −10° respectively. The structural theory predicts three pentanes,  $\text{C}_5\text{H}_{12}$ , and three and only three such compounds are known; they are listed below:

ISOMERIC PENTANES ( $\text{C}_5\text{H}_{12}$ )

NAME	FORMULA	BOILING POINT
<i>n</i> -Pentane	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	36°
Dimethyl-ethyl-methane	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_3$	28°
Tetramethylmethane	$(\text{CH}_3)_4\text{C}$	10°

The student should satisfy himself that no other arrangement of the atoms is possible in these cases.

A rather complicated mathematical formula has been developed for calculating the number of possible isomers of a paraffin hydrocarbon. The results of applying this formula are rather startling as they show that the number of possible isomers mounts rapidly as we proceed up the series. Thus while there are only nine possible isomeric heptanes (all of which are known) there are 366,319 possible isomers with the formula  $\text{C}_{20}\text{H}_{42}$ . Calculation further shows that the number of isomeric hydrocarbons reaches 69,491,178,805,831 when we consider a paraffin hydrocarbon with forty carbon atoms! Needless to

say, only a very small portion of the total number of possible isomers has been prepared in the case of the hydrocarbons containing more than nine carbon atoms.

**Physical Properties.** The lower members of the paraffin hydrocarbons are gases, the members above  $C_4H_{10}$  are liquids, and above  $C_{16}H_{34}$  solids at room temperature. They are all insoluble in water. The boiling points of the *straight-chain compounds* are plotted in Fig. 8. As in the case of the alcohols, the boiling point increases with increasing molecular weight; the rate of increase is greater with the lower members than with the higher (the curve becomes flatter). It is convenient to remember that

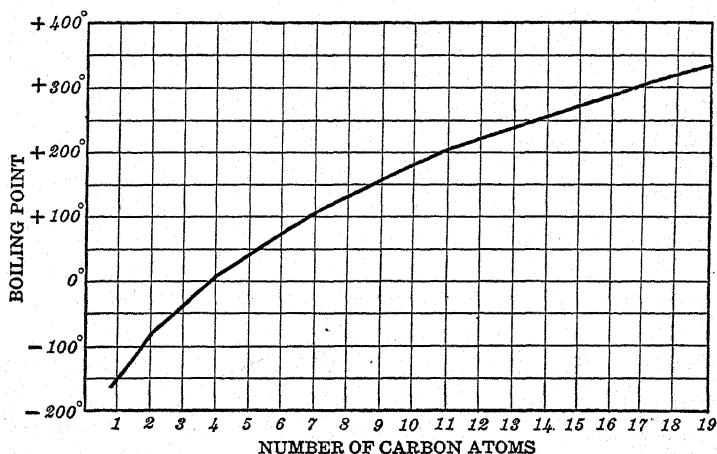


Fig. 8. The boiling points of the normal paraffin hydrocarbons,  $CH_4$  to  $C_{19}H_{40}$ .

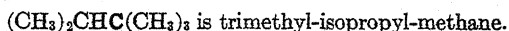
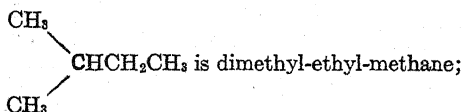
*n*-pentane ( $C_5H_{12}$ ) is the simplest member of the series that is liquid at ordinary temperatures. The highest straight-chain member of the series which has been so far prepared is heptaccontane  $C_{70}H_{142}$ , a solid melting at  $105^\circ$ . The largest paraffin hydrocarbon so far synthesized,  $C_{94}H_{190}$ , has a molecular weight of 1318. It is a chain of 76 carbon atoms to which are attached 18 methyl groups.

In general the straight-chain hydrocarbons have a higher melting point than the branched-chain compounds, and the melting point rises regularly with increase in molecular weight. However, the melting point of a compound is determined by other factors than the molecular weight (for this reason, it is much more difficult to predict melting points than to predict boiling points). In particular the melting point of very symmetrical molecules is almost always surprisingly high. For example, the octane  $(CH_3)_3C - C(CH_3)_3$  is a

crystalline solid at room temperature, melting at  $103^{\circ}$ – $104^{\circ}$  which is only a few degrees below its boiling point ( $106^{\circ}$ ); on the other hand *n*-octane melts at  $-98^{\circ}$ .

**Nomenclature of Paraffins.** The names of the simple members of the series follow the alcohols: *e.g.*, eth-yl alcohol, eth-ane. The five-carbon compound is an exception: instead of the expected "amane" the name pentane is used. From this point on, the number of carbon atoms is denoted by the prefix: thus, hexane,  $C_6H_{14}$ ; heptane,  $C_7H_{16}$ ; octane,  $C_8H_{18}$ ; nonane,  $C_9H_{20}$ ; decane,  $C_{10}H_{22}$ .

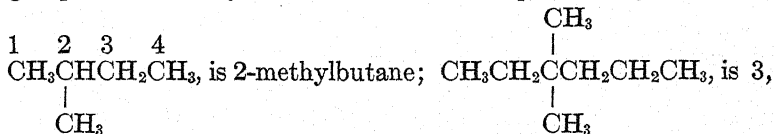
In naming complicated hydrocarbons, a system similar to that employed with the alcohols is often used. It will be recalled that methyl alcohol is considered as the parent substance; similarly, in naming the hydrocarbons, methane is chosen as a basis for the nomenclature. A convenient rule to remember is the following: *the most highly substituted carbon atom is considered the center of the molecule and the alkyl groups attached to it are named.* Thus:



Here we have printed the central carbon atom in heavy type to illustrate the method of nomenclature. This is, of course, not usually done. It is advisable to practise the writing and naming of a variety of hydrocarbons to be certain that one is familiar with the principles employed.

**The Geneva System of Nomenclature.** The naming of complex substances presents many difficulties. Methods of naming simple substances are sufficient for the purposes of our elementary study of the subject, but they do not suffice when more complicated compounds are considered. In 1892 a congress of chemists adopted a systematic scheme of nomenclature. This system has become known as the "Geneva System." The paraffin hydrocarbons are named according to the *longest continuous chain*; the name of the hydrocarbon with this number of carbon atoms is modified by noting what alkyl groups are attached to the chain. The chain is numbered and the position of the substituent alkyl

groups indicated by a number. For example, the hydrocarbon,



3-dimethylhexane and  $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$  is 3-methyl-4-ethylheptane.

The alcohols of the series  $\text{C}_n\text{H}_{2n+1}\text{OH}$  are named as derivatives of the hydrocarbons  $\text{C}_n\text{H}_{2n+2}$ . The terminal ending -ol is added to the name of the parent hydrocarbon, which is always considered as corresponding to the longest chain in the molecule. The following examples illustrate the naming of alcohols by the Geneva system:  $\text{CH}_3\text{CHOHCH}_2\text{CH}_3$  is butanol-2 (the 2 indicates the position of the hydroxyl group),  $\text{CH}_3\text{CHOHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$  is 3-methyl-



pentanol-2. The alkyl halides are named by considering them as chloro, bromo, or iodo derivatives of the paraffin hydrocarbons and indicating the position of the halogen atom by a number; thus, isopropyl bromide,  $\text{CH}_3\text{CHBrCH}_3$  is 2-bromopropane. The system includes all the many types of compounds which are known (e.g., unsaturated hydrocarbons, aldehydes, ketones, acids, cyclic compounds); in each case a hydrocarbon is considered as the parent substance and a characteristic ending of the name shows the reactive group.

**Chemical Properties of Paraffins.** The paraffin hydrocarbons are characterized by their chemical inertness. They do not react with metallic sodium, phosphorus trichloride, bromine water, or potassium permanganate. When ignited in the presence of air or oxygen, they burn; if the proportions of vapor and oxygen are within certain limits, the combustion is explosive. The lower members of the series burn with an almost non-luminous bluish flame. The most important industrial uses of the paraffin hydrocarbons is as a fuel and as a starting point for the manufacture of certain chemicals.

**Heats of Combustion.** The combustion of an organic compound is a strongly exothermic reaction (*i.e.*, heat is evolved). A knowledge of the amount of heat liberated when a particular

substance is burned is of great value in estimating its utility as a fuel. Heats of combustion are also of value in connection with calculations of theoretical interest which are concerned with the forces holding the molecule together. The heat of combustion is determined by burning a weighed quantity of the compound in an excess of oxygen in an apparatus known as a *calorimeter* and determining the amount of heat evolved. The results are usually expressed in kilogram calories (kg. cal.) per mole. If we wish to state how much heat is evolved or absorbed in a given reaction, it is common to express this by writing the amount on the right hand side of the equation. Thus the combustion of gaseous methane is written:



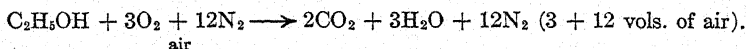
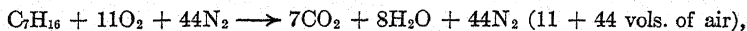
For practical purposes in connection with the fuel value of liquids it is often more important to know the amount of heat evolved in the combustion of a *given weight* of material rather than per mole. In the table below both methods of expressing the results are given for a number of gaseous and liquid paraffin

HEATS OF COMBUSTION

MOLECULAR FORMULA	SUBSTANCE	KILOGRAM CALORIES PER MOLE	KILOGRAM CALORIES PER KILO
(A) <i>Gases</i>			
CH <sub>4</sub>	Methane	210.8	13,200
C <sub>2</sub> H <sub>6</sub>	Ethane	370.4	12,300
C <sub>3</sub> H <sub>8</sub>	Propane	526.3	11,980
C <sub>4</sub> H <sub>10</sub>	Isobutane	683.4	11,780
C <sub>5</sub> H <sub>12</sub>	<i>n</i> -Pentane	838.3	11,620
C <sub>5</sub> H <sub>12</sub>	Isopentane	843.5	11,715
C <sub>2</sub> H <sub>2</sub>	Acetylene	312	12,000
C <sub>2</sub> H <sub>4</sub>	Ethylene	332	11,860
CO	Carbon monoxide	67.2	2,400
H <sub>2</sub>	Hydrogen	68.4	34,200
(B) <i>Liquids</i>			
C <sub>6</sub> H <sub>14</sub>	<i>n</i> -Hexane	990	11,520
C <sub>7</sub> H <sub>16</sub>	<i>n</i> -Heptane	1149	11,499
C <sub>8</sub> H <sub>18</sub>	<i>n</i> -Octane	1305	11,430
C <sub>10</sub> H <sub>22</sub>	<i>n</i> -Decane	1610	11,500
CH <sub>3</sub> OH	Methyl alcohol	170	5,350
C <sub>2</sub> H <sub>5</sub> OH	Ethyl alcohol	328	7,140

hydrocarbons; in the case of the gases the molar basis is equivalent to giving the heat per unit volume of gas (approx. 22 liters N.T.P.). For comparison the heat of combustion of two alcohols, carbon monoxide, and certain other substances are included. It is evident that the heat of combustion *per mole* of the paraffin hydrocarbons increases regularly with increase in the number of carbon atoms. Since the weight of one mole also increases, the heat evolved per kilogram burned is actually somewhat less for propane than for methane but is nearly constant for the higher members of the series. Methyl and ethyl alcohols are clearly much less satisfactory sources of heat than the hydrocarbons, since the heat of combustion is much less either calculated per mole or on a weight basis. Carbon monoxide is inferior to methane on either a gaseous volume or weight basis. Such facts are of great importance to the engineer who wishes to calculate the fuel value of a mixture of gases.

It is an interesting fact that although gasoline has a fuel value of about 10,500 kg. cal. per kilo and ethyl alcohol only 7,140 kg. cal. per kilo, the two yield nearly the same power when used in an internal combustion engine. This is because the amount of power yielded by a given engine is determined by the amount of heat available *per unit volume of combustible mixture in the cylinder*. Now since gasoline is a hydrocarbon mixture with approximately the composition  $C_7H_{16}$  it takes about 3.6 times as much air to burn a given volume of *gaseous* gasoline as is required to burn the same volume of alcohol vapor. This is evident from the following equations (air is taken as  $O_2 + 4N_2$ ):

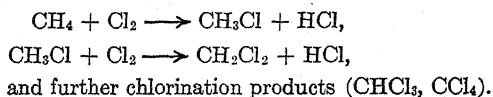


A reference to the table shows that per unit of *gaseous* volume (*i.e.*, per mole), heptane,  $C_7H_{16}$ , evolves on burning about 3.5 times as much heat as alcohol.

This greater output of heat is offset by the fact that about  $\frac{11 + 44}{3 + 12}$  or about 3.6 times as much air is required, and in an automobile cylinder of a given size there is consequently only room for about a third as much gasoline vapor as alcohol. Of course, there are other factors involved in determining what is the best fuel for an internal combustion engine, but on the power basis alone, alcohol is nearly as satisfactory as gasoline.

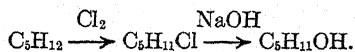
**Halogenation.** The paraffin hydrocarbons react with either bromine or chlorine (but not iodine) in the presence of light; the halogen atoms replace one or more hydrogen atoms. The general reaction is called **halogenation**, a term which includes **chlorination**

(action of chlorine) and **bromination** (action of bromine). These reactions are **substitution reactions**; the hydrogen atom is substituted by a halogen atom. As an example of halogenation the action of chlorine on methane may be given. The reaction is difficult to control, and a mixture of products usually results ( $\text{CH}_3\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ):



**Alcohols from Hydrocarbons.** The first reaction written above should enable us to go from the hydrocarbon, methane, to the alkyl halide, methyl chloride. From this, in turn, we could prepare methyl alcohol. In practice this is difficult, but the reactions have been used in attempting the commercial preparation of methyl chloride from methane. This hydrocarbon is the chief constituent of natural gas in many localities. The presence of strong light favors the reaction, and many patents have been issued for the processes of chlorinating natural gas. With the advent of synthetic methyl alcohol from water gas, this reaction is not of much economic interest.

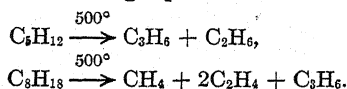
The *halogenation of paraffin hydrocarbons is never used in the laboratory for preparative purposes*, because the reaction forms a great variety of products and is difficult to control. This is also true in industry with the exception of a few processes which include the production of a mixture of amyl alcohols from the isomeric pentanes obtained from natural gas. The pentanes may be separated from the other hydrocarbons present in the gas by a process of condensation and fractionation. The chlorination is controlled so that only one hydrogen atom is replaced. The amyl chlorides, thus formed, are hydrolyzed to the alcohols by the action of sodium hydroxide under special conditions. The steps may be represented as follows:



The mixture of amyl alcohols is known as "pentasol." It is used in the preparation of esters for solvents of lacquer paints (p. 319).

**Thermal Decomposition.** The members of the paraffin series on heating to a high temperature ( $300^\circ$ – $600^\circ$ ) decompose into

smaller molecules. Examples of such reactions (pyrolysis) are represented by the following equations:



In every case a number of different reactions takes place and a great variety of products is formed. Olefin hydrocarbons (Chap. IV) are generally produced during such pyrolytic reactions. Hydrogen, also, is often a product. The structure of the hydrocarbon, the temperature, the pressure, and the presence of catalysts influence the rate of the thermal decomposition and the nature of the products. The significance of these reactions in the production of gasoline has been mentioned earlier in this chapter and will be referred to again.

**Distillation of Petroleum.** Petroleum as it comes from the ground is a rather viscous, highly colored liquid. The first step of refining is essentially a distillation to separate the more volatile from the less volatile materials (see Fig. 9). The lowest boiling portion (below  $70^\circ$ ) is sometimes used in the laboratory as a solvent; it is known as **ligroin** or **petroleum ether**. When obtained from Pennsylvania oil, it is largely composed of pentanes and hexanes. The material which boils between  $85^\circ$  and  $200^\circ$  is usually sold as **gasoline**. **Kerosene** is the next fraction; it usually boils in the range  $200^\circ$ – $300^\circ$ ; it will not take fire directly, but, if allowed to moisten a wick in a suitable lamp, it will burn with a pleasant luminous flame.

The residual oil left after the gasoline and kerosene have been distilled is called "topped crude" or **fuel oil**. It is used as fuel. For the most part, fuel oils are blown out from a nozzle in the form of a fine spray mixed with air or steam. This spray is ignited and gives a hot flame. Locomotives and steamships are often fired with crude oil.

Certain kinds of crude petroleum yield on distillation high-boiling oils which are used as **lubricating oils** and a solid, waxlike material, **paraffin**, used in the manufacture of candles. Such oils are said to have a "paraffin base." From them are also prepared soft greases such as **vaseline**, which is essentially paraffin mixed with some liquid hydrocarbon which has not been removed in the refining. Other varieties of petroleum do not give lubricating oils and paraffin but a thick, black pitch, which is used in roofing

and paving; such oils are called "asphaltic." Pennsylvania petroleum has a paraffin base; Mexican and Californian oils are for the most part asphaltic. "Liquid petrolatum," or "mineral oil," is a carefully refined, high-boiling distillate obtained from certain oils which do not yield paraffin.

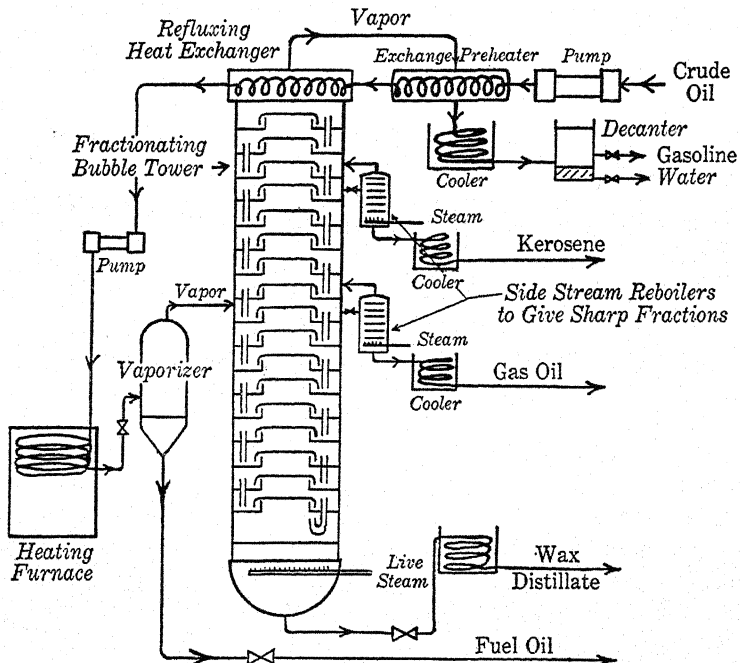


Fig. 9. Diagram of a modern crude oil distillation unit.

It will be noted that the crude oil starts at the upper right hand corner of the diagram and the products are taken off below on the right.

**Petroleum Refining.** The method of further refining petroleum distillates depends on the kind of objectionable components in the fractions. The undesirable materials are olefin hydrocarbons (Chap. IV) which cause gum and tar formation, aromatic hydrocarbons (Chap. XVIII) which when present in high concentration interfere with uniform performance of engines, and sulfur compounds which have bad odors and produce sulfur dioxide when burned.

The elimination of the first two undesirable components is generally brought about by treating the petroleum fraction for a short time in the cold with fairly concentrated sulfuric acid. Under specially controlled conditions, the paraffins and cycloparaf-

fins are unaffected. To remove traces of acid, the fraction is agitated with sodium hydroxide solution. Sulfur compounds are removed by special methods.

Two other methods of refining are now used. In one method the hydrocarbon fraction is extracted with an immiscible solvent which removes the undesirable components. The solvents used are liquid sulfur dioxide,  $\beta$ ,  $\beta$ -dichloroethyl ether (p. 177), furfural (p. 512), and phenol (p. 352). The extraction method is widely used in the refining of lubricating oils and to a less extent for gasoline refining. The other process of refining is to pass the petroleum vapors through a column of natural clay, silica gel, or activated charcoal. In this method the undesirable components are selectively adsorbed from the petroleum mixture.

**Cracking Process.** When petroleum was first refined, kerosene (b.p.  $120^{\circ}$ – $280^{\circ}$ ) was the desired product. Since the advent of the automobile, the important product of the petroleum industry has ceased to be kerosene and has become gasoline. Prior to the use of automobiles, the lower boiling fractions were thrown away or used to dilute the kerosene. Later the difficulty was to produce sufficient gasoline. In spite of the great number of oil fields which have been discovered our supply of gasoline in normal times would be quite inadequate without the gasoline produced by the "cracking" process. The effect of this process on our oil supply is obvious. During 1934 the cracking process produced an amount of gasoline equivalent to the yield from 792 million barrels of crude oil by straight distillations. This quantity of crude oil was about 46 per cent of the total used for all purposes during that year.

There are several different processes for producing gasoline by cracking. In all of them the large molecules of the less volatile constituents of petroleum undergo thermal decomposition (p. 51) producing simpler substances with lower boiling points. Since petroleum itself is such a complex mixture, it is impossible to write an equation representing these reactions. The hypothetical equation written below may be taken as a representative of the types of changes which probably occur.

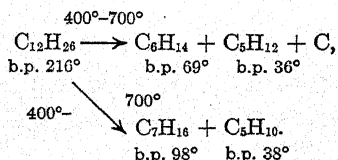


Figure 10 shows the essential parts of the apparatus used in the Dubbs cracking process.

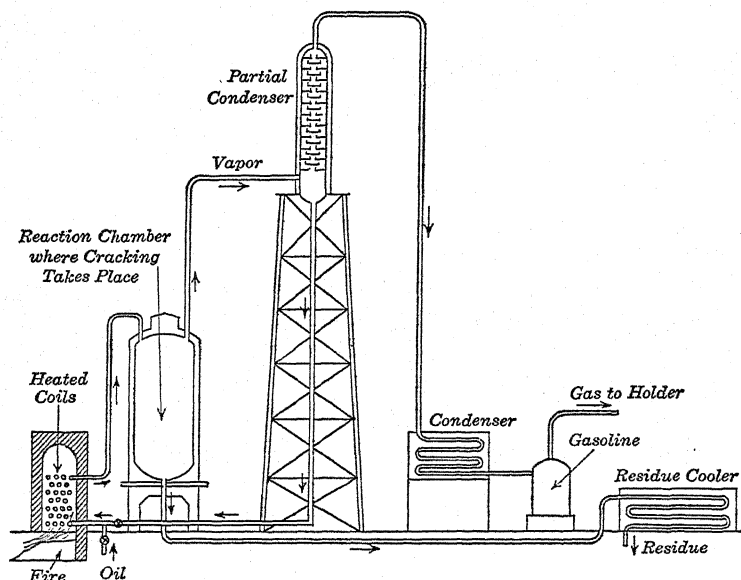


Fig. 10. Simplified diagram of the Dubbs apparatus for cracking petroleum oils.

**By-Products of Cracking.** During the cracking process enormous amounts of gas are formed which consist chiefly of low boiling paraffin hydrocarbons and olefins (Chap. IV). The latter by-product is extremely versatile in its reaction, and it forms the basis of a very large synthetic industry. We shall discuss some of the features of this interesting industry in detail at a later time (Chap. IX).

The manufacture of an exceptionally fine gasoline from cracking gases is of considerable importance. In this method gases rich in olefins are passed over a phosphoric acid catalyst at relatively high temperatures and pressures. Under these conditions a process known as polymerization occurs (p. 76), and a gasoline mixture is formed. The product is referred to as "polymerized gasoline," and it is particularly suited as an aviation fuel.

**Gasoline from Natural Gas.** Considerable gasoline is obtained from natural gas which occurs with petroleum in many fields. The natural gas is usually a mixture of the gaseous members of

the paraffin series but carries as vapor many of the compounds which are liquid at ordinary temperature ( $C_5H_{12}$  -  $C_8H_{18}$ ). By compression, or absorption on charcoal or in heavy oil, it is possible to remove the less volatile vapors from the gas. The **casing-head gasoline** thus produced is relatively low-boiling. It is often mixed (or "blended") with some of the higher boiling gasoline obtained from the distillation of petroleum and called "high test" gasoline.

**Anti-Knock Gasolines.** An internal combustion engine which has a high compression is more efficient than an engine with a low one. High compression engines, however, knock badly with many samples of gasoline. As a result of a great deal of experimentation it has been found that this knocking can be avoided by adding a small amount of lead tetraethyl to the gasoline (p. 29). Gasoline containing lead tetraethyl is sold as "ethyl gas."

It has also been found that the tendency of an engine to knock depends on the nature of the gasoline. Certain branched hydrocarbons and ethylenic hydrocarbons (p. 58) are better in this respect than the normal paraffin hydrocarbons.

Gasolines from certain sources are superior to others in regard to their anti-knock properties. Because of this they are often blended with inferior gasoline in order to improve the performance of the latter.

The *knock rating* of gasoline is determined by using a sample of the gasoline in a special engine of such high compression that it knocks very badly on all except the very best fuels. The knocking is recorded by means of a so-called "bouncing-pin." This is a device whereby every time the engine knocks, a metallic pin rises and evokes an electrical contact; the duration of this contact is proportional to the severity of the knock. A suitable electrical recording system is connected with the bouncing pin. A certain grade of gasoline with very low knocking power may be taken as a standard. Other gasolines are compared with the standard by determining how many cubic centimeters of lead tetraethyl must be added per gallon to reduce the knocking to that of the standard. The greater the amount of lead tetraethyl which must be added the worse the gasoline from the point of view of knocking. By means of such engine tests it has been possible to discover the best sources of gasoline of low-knocking power. In particular it has been possible to control cracking processes so that gasolines with a very low anti-knock rating can be produced.

**Gasoline Antioxidants.** The presence of small amounts of ethylenic hydrocarbons (p. 58) in gasoline is desirable because of their anti-knock properties. However, such a gasoline on standing develops undesirable colors and gums which impair its

efficiency as a motor fuel. This change is due to a peculiar air-oxidation, since when stored under nitrogen, the gasoline is perfectly stable. It was found that the addition of minute quantities of certain amino-phenols and other substances (Chap. XXI) checks the tendency of such gasoline to undergo gum formation; such substances are called **inhibitors** or **antioxidants** (Chap. XXIII). Today nearly all gasolines contain inhibitors.

**Motor Fuels from Coal.** There are two industrial processes for the production of motor fuels from coal. They are used mainly in countries which do not have large deposits of crude oil. It is very probable that as the world's oil supply is depleted, these processes will become more important.

In one process carbon monoxide, prepared from coke by the water-gas reaction (p. 13), is allowed to react with hydrogen at high temperatures and atmospheric pressure in the presence of special catalysts. The petroleum so obtained is a mixture of straight and slightly branched hydrocarbons. This reaction is reminiscent of the synthesis of higher alcohols from carbon monoxide and hydrogen (p. 18). It again illustrates the fact that the conditions at which a reaction is carried out are of greatest importance, and furthermore that in many instances the course of the reaction may be changed by altering the conditions (compare with p. 32).

The other important method of petroleum production essentially consists in suspending coal dust mixed with an iron catalyst in oil, pitch, or asphalt, heating the mixture to 400° C., and passing in hydrogen at a pressure of 100–200 atmospheres. The reactions involved are very complicated. Coal is not merely carbon but a complex mixture of organic compounds of high molecular weight together with elementary carbon. The combination of these compounds with hydrogen takes place under the influence of the catalyst; cracking also occurs and eventually a variety of hydrocarbons are formed. These can be fractionated into material suitable for use as gasoline and into lubricating oils. It is reported that from one ton of soft coal 90–140 gals. of low boiling material corresponding to gasoline may be obtained.

### QUESTIONS AND PROBLEMS

1. Describe briefly the refining of petroleum including a discussion of the process of "cracking."
2. Write structural formulas for: diethyl-*n*-propyl-methane; tetramethyl-methane; *n*-octane; dimethyl-diethyl-methane; isobutane; 2, 3-dimethyl-pentane.
3. Name the following: (a)  $(\text{CH}_3)_2\text{CHCH}(\text{CH}_3)_2$ ; (b)  $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_3$ ; (c)  $(\text{CH}_3)_2\text{CHC}(\text{CH}_3)(\text{C}_2\text{H}_5)_2$ ; (d)  $(\text{CH}_3\text{CH}_2)_2\text{CHCH}_3$ .
4. Write balanced equations showing: (a) laboratory method of preparing propane from *n*-propyl bromide; (b) the preparation of ethane from methyl iodide.
5. Write structural formulas for all the isomeric hydrocarbons of the formula  $\text{C}_6\text{H}_{14}$ . Name as many of these as you can.

6. To what series do the following hydrocarbons belong: (a)  $C_8H_{18}$ ; (b)  $C_{24}H_{50}$ ; (c)  $C_7H_{14}$ ?
7. With the aid of equations show how you could prepare the following hydrocarbons from *n*-butyl alcohol: (a) butane, (b) *n*-octane.
8. Why is methane a valuable constituent of illuminating gas? What properties of methane make it desirable in illuminating gas?
9. List four methods of preparing methane, illustrating with equations.
10. Which of the following reagents would you expect to react with *n*-pentane: (a) conc.  $H_2SO_4$ , (b) strong KOH, (c) oxidizing agents, (d) chlorine, (e) iodine?
11. Explain why alcohols are not generally prepared from paraffin hydrocarbons.
12. Calculate the heat evolved when 100 liters (N.T.P.) of (a) water gas ( $H_2 = 50$  per cent,  $CO = 50$  per cent) and (b) natural gas (assume it to be pure isobutane) is completely burned. Calculate the heat evolved per 100 liters of the mixture of gas and sufficient air for combustion to carbon dioxide and water. Compare the results.
13. Why is a Bunsen burner designed for water gas unsatisfactory when used with natural gas?

## CHAPTER IV

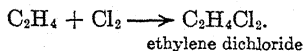
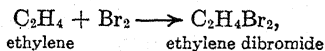
### UNSATURATED HYDROCARBONS

In the cracking of petroleum oils, large amounts of hydrocarbons are usually formed which are not members of the paraffin series. These hydrocarbons combine with bromine and chlorine, and are therefore spoken of as *unsaturated hydrocarbons*. The paraffins do not have this property and, therefore, are called *saturated hydrocarbons*. The unsaturated hydrocarbons always contain less hydrogen than the corresponding paraffins. Because the products of the action of chlorine on the unsaturated hydrocarbons were oily liquids, these hydrocarbons were called "olefiant" or "oil making" hydrocarbons. The word olefiant was later changed to olefin.

#### OLEFINS

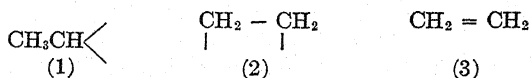
The simplest unsaturated hydrocarbons are the members of the olefin or ethylene series. They have the general formula  $C_nH_{2n}$ ; the first member is **ethylene**,  $C_2H_4$  (a gas b.p.  $-104^\circ$ ), the next **propylene**,  $C_3H_6$  (b.p.  $-47^\circ$ ). It will be noted that they contain two less hydrogen atoms than the corresponding members of the methane series (ethane  $C_2H_6$ , propane  $C_3H_8$ ).

**The Structure of Ethylene.** The olefins combine with bromine or chlorine in such a way that a dibromide or dichloride is formed by the addition of two atoms of the element. Thus with ethylene the equation for the reaction is:



This is an **addition reaction**. A chemical study of the products has shown that they must have the structural formulas  $CH_2BrCH_2Br$  and  $CH_2ClCH_2Cl$ , respectively. The evidence for this will be presented in a later chapter (p. 127). For the present, let us assume that the formula of ethylene dibromide is correct and consider the structure of the hydrocarbon.

If we attempt to write a structural formula for ethylene, we are confronted by the following possibilities:



Formulas 1 and 2 may also be written as  $\text{CH}_3\text{CH}$  and  $\text{CH}_2\text{CH}_2$ . The "free bonds" merely express our knowledge that carbon *may* have a valence of four. Corresponding to formula 1 we would write  $\text{>PCl}_3$  for phosphorus trichloride since we know that phosphorus *may* take on 5 atoms as in  $\text{PCl}_5$ .

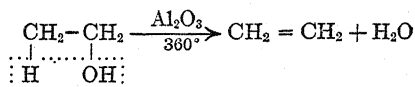
Since ethylene dibromide has the structure  $\text{CH}_2\text{BrCH}_2\text{Br}$  formula 1 is ruled out, because such a substance would add bromine, forming  $\text{CH}_3\text{CHBr}_2$ . If formula 2 were correct, one would expect to find other compounds containing a trivalent carbon atom, for example,  $\text{CH}_3\text{CH}_2\text{CH}_2-$  (or  $\text{CH}_3\text{CH}_2\text{CH}_2$ ). One would further expect that the compound represented by formula 2 would add one atom of bromine, forming  $\text{CH}_2\text{BrCH}_2-$  (or  $\text{CH}_2\text{BrCH}_2$ ) and then later another atom. Such "stepwise" addition has never been noted. With the exception of certain very special cases considered in Chap. XXIV, we know of no compounds containing trivalent carbon. Free methyl,  $\text{CH}_3$ , or free ethyl,  $\text{C}_2\text{H}_5$ , have never been isolated though they are capable of existing in the gaseous state for a very short time. In every case where one might be inclined to write a carbon atom with only three bonds, the *apparently trivalent* carbon atoms occur in pairs side by side. There is, therefore, every reason to believe that, in some way, the missing valences of the carbon atoms are bound to each other. We indicate this opinion by writing a double bond.

The double bond is a convention signifying to the organic chemist the existence of two carbon atoms, side by side, each of which may add an additional monovalent atom or group. The double linkage is often spoken of as a point of *unsaturation*. Compounds with a double bond enter into many reactions in which they pass into compounds with a single linkage.

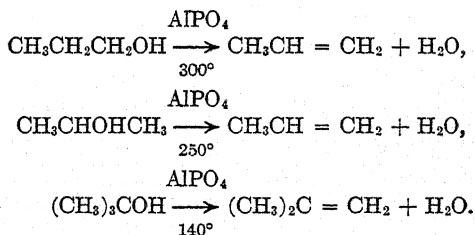
**Preparation of Olefins.** The methods of preparing olefin hydrocarbons enable us to start with our common alcohols or substances easily made from them. All these reactions may be considered as elimination reactions; two atoms or groups are "split out" from the molecule leaving a double bond in their place. The first method given below was used for preparing

ethylene on a large scale during the World War in connection with the synthesis of a war gas, — "mustard gas."

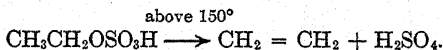
**Dehydration of Alcohols.** In the preparation of ethylene, alcohol vapor is passed through a hot tube containing aluminum oxide or through a tower of coke impregnated with glacial phosphoric acid. These catalysts cause the dehydration of the alcohol:



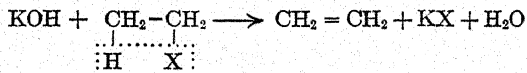
This is a general and excellent method of preparing a great variety of olefins. Primary, secondary, and tertiary alcohols may be employed and, depending on the nature of the alkyl groups attached to the carbinol carbon atom, different substituted ethylenes will be formed. At lower temperatures (250°) the primary alcohols yield ethers, as was noted on page 34. Tertiary alcohols are particularly easy to dehydrate because the catalysts are effective at a relatively low temperature; secondary alcohols in this respect fall between primary and tertiary alcohols. A few examples are as follows:



An indirect method of dehydrating alcohols is to treat them with sulfuric acid; the ester thus formed on heating usually decomposes with the formation of an olefin and sulfuric acid. This older method is now largely superseded by the catalytic method. It is illustrated by the following example:



**Preparation from Alkyl Halide.** An alcoholic solution of potassium or sodium hydroxide acts on an ethyl halide as follows:

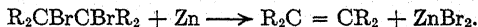
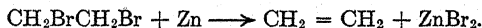


It will be noted that in the production of ethylene by this method, hydrogen iodide has been eliminated from the molecule of ethyl iodide. In general it has been found that by the action of strong alkalis at elevated temperatures all alkyl halides which have a hydrogen atom adjacent to the halogen atom lose a molecule of halogen acid. Another example of this reaction is the following:

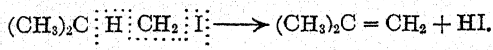


Just as the tertiary alcohols are catalytically dehydrated at a lower temperature than secondary or primary, so too the corresponding halides react more rapidly with alkalis with the formation of unsaturated hydrocarbons. It should be noticed that the elimination of halogen acids from alkyl halides and also of water from alcohols to form olefins takes place between two adjacent carbon atoms, and therefore can occur only when these elements are present on adjacent carbon atoms.

**Preparation from Dihalides.** The addition product of an olefin and bromine gives up its bromine atoms when treated with zinc. This is a convenient laboratory method of preparing ethylene and is a general method for all olefins:



One might be tempted to imagine that in the elimination of halogen acid from alkyl halides or the elimination of bromine from the dibromide a very simple mechanism is involved. Thus it might be thought that the function of the inorganic reagent was merely to combine with free halogen acid or free bromine slowly liberated from the organic halide. This is clearly *not* the case in general, however, for otherwise it would make no difference what alkali were used to combine with the acid or what metal to take up the halogen. Actually it makes a great deal of difference. For example, primary alkyl halides will not form olefins when heated with sodium carbonate (or a base of similar strength) although such a base would neutralize a halogen acid as well as sodium hydroxide. Metallic mercury combines rapidly with free bromine but it is not effective in removing bromine from most dibromides even at an elevated temperature. The actual mechanism of all these reactions is complicated and not fully understood; very probably there are several paths which lead to the same product. In an elementary course it is very usual to write such diagrams as the following:



The student should be on his guard lest he confuse such a pictorial representation with the real mechanism of the reaction which is often much more complex.

**Physical Properties of Isomeric Olefins.** The number of isomers in the olefin series is much greater than with the paraffins. This is illustrated by comparing the number of butylenes and amylenes with the corresponding paraffin derivatives.

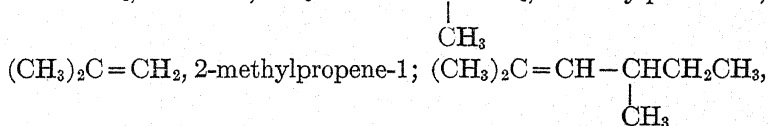
BOILING POINTS OF THE SIMPLER ETHYLENE HYDROCARBONS

MOLECULAR FORMULA	NAME	STRUCTURAL FORMULA	BOILING POINT
$C_2H_4$	Ethylene	$CH_2 = CH_2$	$-104^\circ$
$C_3H_6$	Propylene	$CH_3CH = CH_2$	$-47^\circ$
<i>Isomeric Butylenes</i>			
$C_4H_8$	Sym. dimethylethylene	$CH_3CH = CHCH_3$	$+1^\circ$
	Unsym. dimethylethylene	$(CH_3)_2C = CH_2$	$-6.6^\circ$
	Ethylethylene	$CH_3CH_2CH = CH_2$	$-6.7^\circ$
<i>Isomeric Amylenes</i>			
$C_5H_{10}$	Sym. methylethylethylene	$CH_3CH = CHCH_2CH_3$	$+36^\circ$
	Unsym. methylethylethylene	$CH_3CH_2(CH_3)C = CH_2$	$32^\circ$
	<i>n</i> -Propylethylene	$CH_3CH_2CH_2CH = CH_2$	$39^\circ$
	Isopropylethylene	$(CH_3)_2CHCH = CH_2$	$20^\circ$
	Trimethylethylene	$(CH_3)_2C = CHCH_3$	$38^\circ$

A comparison of this table with the one on page 40 shows that the boiling points of the olefins are very close to those of the corresponding paraffins. Two hydrogen atoms make very little difference in this physical property. Like all other hydrocarbons the olefins are insoluble in water.

**Nomenclature.** Above *amylenes* (the name of this hydrocarbon should be particularly noted), each group of isomers is named from the paraffins, the ending -ane being changed to -ylene: thus, hexylene, heptylene. The isomeric members of a group are often named as alkyl derivatives of ethylene as in the table. Compounds of the type  $RCH = CHR'$  are called symmetrical; those of the type  $R_2C = CH_2$  unsymmetrical. This system is satisfactory for simple compounds but is unsuited for naming more

complex compounds. For this purpose, the Geneva system should be employed. By this system, the longest carbon chain is named as in the case of the saturated hydrocarbons, but the ending is changed from *ane* to *ene*. The position of the alkyl groups is denoted as in the case of the saturated hydrocarbons; the position of the double bond is shown by a number following the name. This number indicates the *lowest numbered carbon atom involved in the double linkage*. The numbering is always begun at the end of the chain nearest the double bond. The following examples illustrate the method:  $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2$ , butene-1;  $\text{CH}_3\text{CH}=\text{CHCH}_3$ , butene-2;  $\text{CH}_3\text{CH}=\text{CHCHCH}_3$ , 4-methylpentene-2;



2, 4-dimethylhexene-2.

**Ethylene.** The first member of the olefin series is a colorless gas with a characteristic sweetish odor. It burns with a luminous, smoky flame. With air or oxygen it forms a highly explosive mixture. It is usually present in illuminating gas to the extent of a few per cent.

Ethylene is obtained today from the gases liberated during the cracking process in gasoline production (p. 53). It is also produced from natural gas, which is a mixture of gaseous paraffins, by cracking under special conditions. The separation of ethylene from the other products is readily accomplished.

Ethylene is used by growers of citrus fruits since it hastens ripening. Exposure of a green-colored fruit to an atmosphere of ethylene develops the highest yellow or orange color. Ethylene also finds use as an anesthesia and in some respects it is superior to ether.

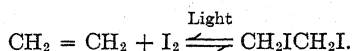
**Chemical Properties.** In contrast with the paraffins the olefins are very reactive. They combine with a great variety of substances, forming derivatives of the paraffin hydrocarbons. We will consider four reactions.

**Addition of Halogens and Hypohalogen Acids.** Chlorine and bromine combine with the members of the olefin series:



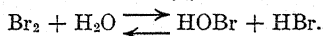
With iodine the reaction is very slow except in the presence of

strong light. Under suitable conditions of illumination an equilibrium is reached which may be approached from both sides:

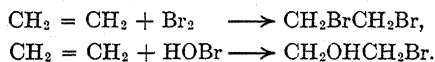


At temperatures of 100°–150° (in the gas phase) the reaction between ethylene and iodine is rapid, but the equilibrium is very unfavorable to the formation of the di-iodide. The reaction between halogens and unsaturated hydrocarbons may be carried out in some inert solvents, such as carbon tetrachloride ( $\text{CCl}_4$ ) or carbon disulfide ( $\text{CS}_2$ ) or in water.

In the latter solvent, another reaction also takes place at the same time. An aqueous solution of bromine or chlorine always contains some hypobromous or hypochlorous acids:

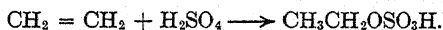


These hypohalogen acids also add to the double linkage. Thus, if ethylene is passed into bromine water, both reactions written below take place:

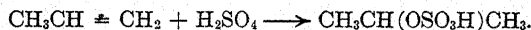


By controlling the concentration of the halogen and the acidity, it is possible to make the last reaction predominate. The preparation of  $\text{CH}_2\text{ClCH}_2\text{OH}$ , ethylene chlorohydrin, is now carried out commercially (p. 173).

**Addition of Acids.** Ethylene is absorbed by warm concentrated sulfuric acid. The other members of the series react even at room temperature. The product is an alkyl sulfuric acid which we have already met a number of times (pp. 30, 60).



If propylene is employed, it has been found that the chief product is the *isopropyl* ester of sulfuric acid. *In general, with an unsymmetrical olefin, the acid group goes to the carbon holding the least number of hydrogen atoms:*

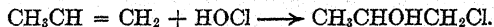


The halogen acids also add to olefin hydrocarbons, forming alkyl halides. The reaction proceeds most rapidly with the higher members of the series and with hydrogen iodide or bromide more rapidly than with hydrogen chloride.



The addition of unsymmetrical reagents, like the halogen acids, to unsymmetrical derivatives of ethylene raises a problem concerning the *mode* of addition. Thus, in the example given above, isopropyl iodide and not *n*-propyl iodide is formed; the halogen atom becomes attached to the central carbon atom, not to the terminal one. What general laws govern the mode of addition in such cases? In the case of the unsaturated hydrocarbons, it has been found that in general the rule given above is valid in regard to the major product of the reaction. This rule, which is often called **Markownikoff's rule**, states that the *halogen atom or acid group becomes attached to the carbon holding the least number of hydrogen atoms*. Careful experiment has shown that in many cases a small amount of the isomer, formed by the other mode of addition, is also produced, the ratio of the two isomers depending to some extent on the nature of the solvent. It should be carefully noted that this rule applies only to hydrocarbons; we shall see in a later chapter that in the case of certain unsaturated acids, esters, and ketones another principle is involved.

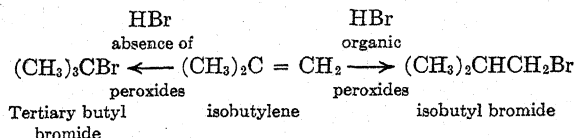
When we consider the mode of addition of the hypohalogen acids to unsymmetrical derivatives of ethylene, we find that here it is the OH group and *not* the halogen atom which joins the carbon holding the fewest hydrogen atoms. Thus:



Here again the rule predicts only the major product; some of the isomer is often formed. A common explanation of the fact that the halogen atom in the halogen acids and hypohalogen acids behave differently is to consider that in the one case the halogen is negatively charged as compared to the hydrogen ( $\text{H}^+\text{Br}^-$ ); in the other it is positively charged with respect to the OH group ( $\text{HO}^+\text{Br}^-$ ). One can then say that the *negative* atom or group attaches itself to the most substituted carbon atom. Although hydrobromic acid dissociates into ions which carry the appropriate charges required by this explanation, there is no evidence that hypobromous acid dissociates to form a positive bromine ion; it actually forms the ions  $\text{H}^+$  and  $\text{OBr}^-$ . Nevertheless, it may be that within the undissociated molecule there tends to be a distribution of electrons which corresponds to the symbol  $\text{HO}^+\text{Br}^-$ .

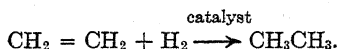
It has been found that the mode of addition of halogen acids to simple olefin hydrocarbons containing a terminal carbon-carbon double bond may be reversed by the addition of organic peroxides (p. 419). During ordinary manipulations, or better still in the presence of antioxidants (p. 403), isobutylene and hydrogen bromide give tertiary butyl bromide in accordance with Markownikoff's rule. On the other hand, however, if organic peroxides are

present (p. 419), isobutylene bromide predominates in the product. The following reactions summarize these facts:



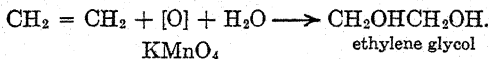
**Hydrogenation.** The double bond may be saturated with hydrogen by a process known as **catalytic hydrogenation**.

In this process the hydrocarbon, alone or in solution with an inert solvent, is shaken with hydrogen in the presence of highly active forms of platinum or palladium. These catalysts in some way cause the hydrogen to combine with the unsaturated hydrocarbons. Less expensive but also less effective is finely divided nickel whose use generally requires both high temperatures and pressures or a vapor phase reduction. However, a highly active nickel catalyst can be made which will bring about the hydrogenation of many ethylenic hydrocarbons in the cold. With ethylene the reaction may be written as follows:



The catalytic hydrogenation of olefin hydrocarbons provides another method of preparing pure members of the paraffin series.

**Oxidation.** Olefins are oxidized by potassium permanganate ( $\text{KMnO}_4$ ) to compounds containing two hydroxyl groups. The hydrocarbon is shaken with the permanganate solution. The equation<sup>1</sup> for the reaction with ethylene is:



The product is **ethylene glycol**; it is further oxidized to carbon dioxide and water if the solution is warm and concentrated. In the case of substituted ethylenes the final products of oxidation are usually one or two molecules of organic acids having the general formula  $\text{RCOOH}$ . Isomeric olefins on oxidation yield different acids, and this fact has enabled the chemist to determine the position of the double linkage. For example,  $\text{CH}_3\text{CH}_2\text{CH} = \text{CH}_2$  on oxidation yields  $\text{CH}_3\text{CH}_2\text{COOH}$ , while  $\text{CH}_3\text{CH} = \text{CHCH}_3$  on oxidation yields two molecules of  $\text{CH}_3\text{COOH}$ .

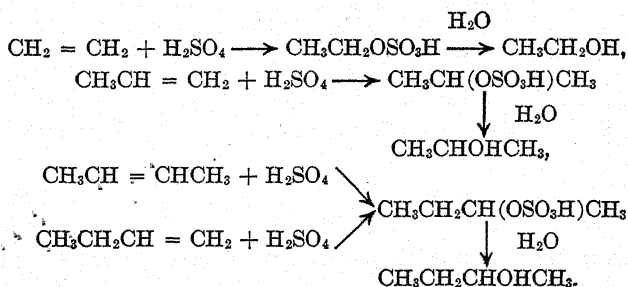
<sup>1</sup> The symbol  $[\text{O}]$  will be used throughout this book to indicate oxygen from an oxidizing agent; the oxidizing agent is written beneath.

## SYNTHESES FROM PETROLEUM AND NATURAL GAS

The gases obtained as by-products in the cracking of petroleum and natural gas are rich in unsaturated hydrocarbons such as ethylene, propylene, and the isomeric butylenes. As a result of extensive investigations in the last few years, methods have been developed for converting some of these substances into products of great value.

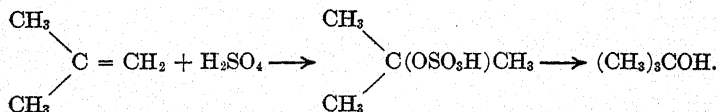
**Alcohols from Olefins.** We have just seen that the olefins react with sulfuric acid to form alkyl sulfuric acids. These on hydrolysis yield the alcohols.

Today a large amount of ethyl alcohol is made commercially by this process from ethylene (p. 16). In addition to this, isopropyl alcohol is manufactured from propylene, and secondary butyl alcohol from the two normal butenes:



Both these once rare alcohols have been made in tank-car quantities from the gaseous by-products of the cracking of petroleum (p. 53).

Tertiary alcohols result from the branched olefins; isobutylene yields tertiary butyl alcohol:



In all these reactions no attempt is made to isolate the intermediate alkyl sulfuric acid; the absorption of the gaseous hydrocarbon and the hydrolysis are carried out in one process. The essential parts of the apparatus employed are shown in Fig. 11. The alcohols are obtained by distilling the reaction mixture. The mixture of olefins can be separated by a process of liquefaction or by careful control of the conditions in the reaction with

sulfuric acid, since certain of the olefins react faster than others. The kind of oil and the cracking process also influence the composition of the gases. By control of all these variables it is possible to limit the number of alcohols produced in one reaction and thus simplify the problem of purification.

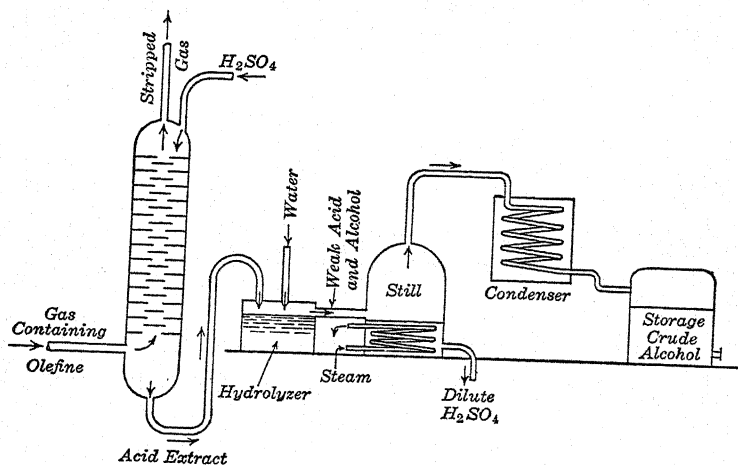


Fig. 11. The essential parts of the apparatus used in the preparation of alcohols from unsaturated hydrocarbons.

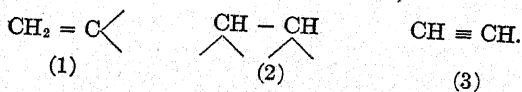
Although the over-all reaction of the synthesis of an alcohol from an ethylenic hydrocarbon is the addition of water, the direct hydration of these hydrocarbons in the gas phase is not yet commercially feasible. This reaction is now the subject of extensive research, and it is probable that under proper conditions and with solid catalysts direct hydration of olefins will become an industrial reality.

#### ACETYLENIC HYDROCARBONS

This class of hydrocarbons has the general formula  $C_nH_{2n-2}$ . The first member of this series, acetylene  $C_2H_2$ , is by far the most important.

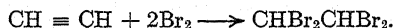
**Structure of Acetylene.** Acetylene reacts with bromine and chlorine forming a compound  $C_2H_2X_4$  which, in the case of the bromide, has the structure  $CHBr_2CHBr_2$ .

The possible formulas for acetylene,  $C_2H_2$ , are:



The first two, of course, may be written also as  $CH_2 = C$  and

CH — CH. The structure of the tetrabromide shows that we must write formula 2 or 3. The reasons for preferring 3 are similar to those given in favor of the double-bonded formula for ethylene (p. 59). Compounds of the type  $\text{CH}_3\text{CH}_2\text{CH} \ltimes$  are unknown; with the exception of carbon monoxide and a few other peculiar substances, no compounds containing divalent carbon have been prepared. We therefore use a triple bond to signify the existence of two apparently divalent carbon atoms side by side. We believe that the valences are in some way joined with one another. Such compounds have the ability to add *four* monatomic atoms or groups, as the following reaction indicates:

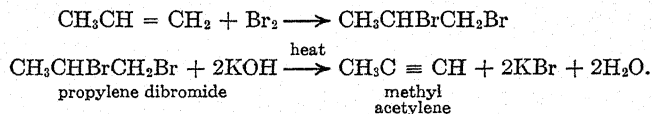


**Preparation of Acetylenic Hydrocarbons.** Acetylene is easily prepared on a large scale from calcium carbide,  $\text{CaC}_2$ , and water:



Since calcium carbide is readily made in the electric furnace from coke and lime, acetylene is one of the cheap organic chemicals available to the industrial chemist.

Acetylene and its homologs may be prepared by eliminating two molecules of halogen acid from a dihalide by means of molten alkali or strong solutions of potassium hydroxide. The dihalide in turn can be made from the corresponding olefin and halogen.



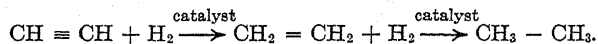
**Acetylene.** Acetylene is a colorless gas, insoluble in water, with a characteristic odor. It can be condensed to a liquid which boils at  $-84^\circ$  and which is explosive if subjected to a sudden shock. For its transport it is necessary to dissolve the gas under pressure in acetone. In this form it is perfectly safe. It burns with a luminous flame when a specially constructed burner is used which allows free access of air.

Acetylene has had a varied industrial history. It was first used at the end of the last century as a lighting gas in competition with coal gas. Acetylene lamps were at one time used as bicycle and automobile lights.

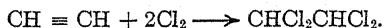
The present industrial use of acetylene is as a cheap raw material

from which to prepare other compounds (Chap. VII). The preparation of an artificial rubber from acetylene is discussed at the end of this chapter.

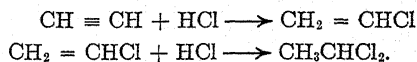
**Addition Reactions of Acetylene.** The triple linkage in acetylene will add four monovalent atoms or groups, much as the double linkage in ethylene adds two such atoms or groups. In a few reactions, only two atoms or groups can be added and a derivative of ethylene is formed. Thus, if acetylene is passed into a water solution of chromous chloride,  $\text{CrCl}_2$  (a powerful reducing agent), ethylene is formed. Certain other reducing agents enable one to prepare ethylene derivatives from acetylenic hydrocarbons. However, since ethylene and its derivatives are also reactive, usually the addition reactions do not stop at the ethylene stage. The catalytic hydrogenation of acetylene produces ethane if sufficient hydrogen is employed:



With chlorine, tetrachlorethane  $\text{CHCl}_2\text{CHCl}_2$  is the final product:

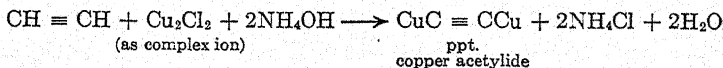


The reaction between acetylene and dilute sulfuric acid yields a valuable compound, acetaldehyde. This will be considered in Chap. VII. The halogen acids add to acetylene forming a halogen derivative of ethylene which can then combine further with another molecule; the final product has two halogen atoms on the same carbon atom.

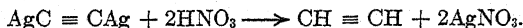


The addition of acids to homologs of acetylene follow the same rules as in the case of unsymmetrical olefins (p. 65).

**Acetylides.** Acetylene and the members of the acetylene series which contain the grouping  $-\text{C} \equiv \text{CH}$ , enter into two peculiar and characteristic reactions. When shaken with ammoniacal cuprous or silver solutions, they form precipitates of **metallic acetylides**. These are usually highly explosive in the dry state. The acetylides are related to acetylene as salts are to acids. The metal has replaced a hydrogen atom. These reactions are illustrated by the following equations:

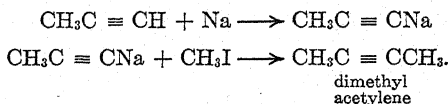


On treatment with dilute acids, the acetylides regenerate acetylene:

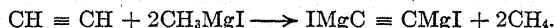


Sodium acetylide  $\text{CH} \equiv \text{CNa}$  is formed by the action of acetylene on a solution of sodium in liquid ammonia or by passing the gas through molten sodium at  $180^\circ$ . Disodium acetylide,  $\text{C}_2\text{Na}_2$ , can also be formed in this way. The sodium acetylides are colorless solids which are decomposed by water with the formation of acetylene.

The sodium acetylides offer another method of preparing homologs of acetylene. They react with alkyl halides in the following manner using liquid ammonia as the solvent:



Acetylene liberates methane from methyl magnesium iodide when it is passed into an ethereal solution of this reagent:

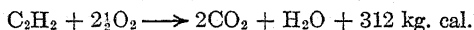


**Nomenclature.** According to the Geneva system acetylenic hydrocarbons are named by changing the ending *ane* of the saturated hydrocarbon to *ine* or *yne*; the position of the unsaturation is indicated as in the case of the olefins by a numeral after the name. They are also named as alkyl derivatives of acetylene. Thus  $\text{CH}_3\text{C} \equiv \text{CH}$  is propine (also written propyne) or methylacetylene; it is a gas boiling at  $-23^\circ$ .  $\text{CH}_3\text{C} \equiv \text{CCH}_3$  is dimethylacetylene or butine-2; it boils at  $28^\circ$ .  $\text{CH}_3\text{CH}_2\text{C} \equiv \text{CH}$  is ethylacetylene or butine-1 (b.p.  $14^\circ$ ).

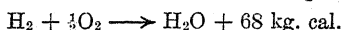
**Heats of Combustion and Formation.** The heat evolved by the combustion of a gram mole of acetylene is somewhat less than in the case of ethane; the value is 312 kg. cal. instead of 370 kg. cal. However, there are only two hydrogen atoms in acetylene to unite with oxygen, while ethane has six. Therefore one might expect that the heat of combustion of acetylene would be much less than that of the hydrocarbon richer in hydrogen. The fact that they are so nearly the same shows that the acetylene molecule is proportionally richer in energy than ethane. This fact is expressed quantitatively by calculating the heat change which *would be produced* if the hydrocarbon could be prepared directly from solid carbon (graphite) and gaseous hydrogen. This number is known as the **heat of formation**; for ethane it is 23 kg. cal., for acetylene  $-56$  kg. cal. The value for ethylene is between that of the other two; it is  $-7.5$  kg. cal.

The difference in the sign of the heat of formation of the saturated and unsaturated hydrocarbons means that in the one case heat would be evolved in their formation from the elements and in the other case heat would be absorbed. Acetylene is said to be a strongly *endothermic compound*; it has more energy than the elements of which it is composed. It is this extra energy which is released on its combustion which makes it have so surprisingly high a heat of combustion. It is also this excess of energy which is released when liquid acetylene explodes, which it does, if subjected to sudden shock.

The heat of formation of a compound can not be measured directly as organic compounds can not be prepared from the elements or converted into them by any simple reaction. The heat of formation is calculated from the heat of combustion of the compound and the heat of combustion of solid carbon and gaseous hydrogen. This is illustrated by the following thermochemical equations which apply to the case of acetylene:



The products of combustion,  $2\text{CO}_2$  and  $\text{H}_2\text{O}$ , are formed from the elements by the liberation of  $188 + 68 = 256 \text{ kg. cal.}$



This quantity is 56 kg. cal. *less than* the amount liberated, when a gram mole of acetylene is burned. Therefore 56 kg. cal. of heat would be absorbed if we prepared one mole of gaseous acetylene from solid carbon and gaseous hydrogen. The heat of formation is therefore  $-56 \text{ kg. cal.}$

#### DIOLEFINS

X A class of hydrocarbons isomeric with the acetylenic series is the diolefin series,  $\text{C}_n\text{H}_{2n-2}$ . The members of this series contain two double linkages; the simplest member is *allene*,  $\text{CH}_2 = \text{C} = \text{CH}_2$ , a gas boiling at  $-32^\circ$ .

**The Butadienes.** Among the most interesting and useful members of the diolefin series are the derivatives of butadiene-1, 3,  $\text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2$ . All these compounds contain two double linkages connected by a single bond. *Such a system of alternate single and double linkages* is known as a *conjugated system of double bonds*. Compounds containing conjugated systems undergo a number of special reactions; one of these, the polymerization reaction, will be discussed shortly in connection with rubber.

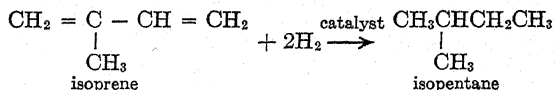
The nomenclature of the diolefins is in accord with the Geneva system. The longest straight chain is named, the ending *diene* replacing the *-ane* of the saturated hydrocarbon. The position of the two double linkages is indicated by two numerals. Thus  $\text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2$  is butadiene-1, 3; while on the other hand  $\text{CH}_2 = \text{C} = \text{CHCH}_3$  would be butadiene-1, 2.

Butadiene-1, 3 is a gas which condenses at  $-4^{\circ}$ . 2-Methylbutadiene-1, 3 (isoprene) boils at  $34^{\circ}$  and 2, 3-Dimethylbutadiene-1, 3 boils at  $70^{\circ}$ .

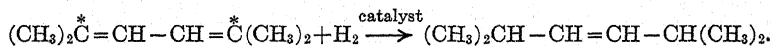
**Structure of the Diolefins.** Like the acetylenes, the diolefins combine with four monovalent atoms or groups forming derivatives of the paraffin hydrocarbons. Unlike the acetylene series, however, the groups which have been added are distributed on *four different* carbon atoms. For this reason we write a structure with *two double bonds*:



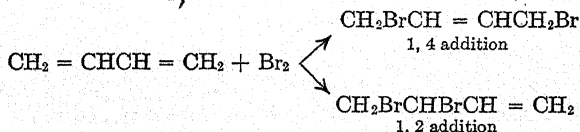
The diolefins take up two molecules of gaseous hydrogen when subjected to catalytic hydrogenation and are thus converted into the paraffin hydrocarbons. This reaction enables us to prove the way in which the carbon chain is arranged in any diolefin of unknown structure. For example, isoprene on hydrogenation yields isopentane:



**Special Reactions of Conjugated Dienes.** The reactions of conjugated dienes are of extreme interest since they demonstrate the effect of two pairs of double bonds on each other especially if they are conjugated. Thus, when some of the homologs of butadiene are allowed to react catalytically with hydrogen, and the reaction is stopped after one mole of hydrogen is absorbed, the product obtained indicates a special type of addition:



In this reaction one hydrogen atom has added to each carbon at the end of the conjugated system (marked by asterisks), and a double bond is formed between the center carbon atoms. This type of addition is known as **1, 4 addition to conjugated systems**. In many addition reactions of such diolefins a mixture of products formed by 1, 4 addition to the conjugated system and 1, 2 addition to one of the double bonds is obtained. The reaction of butadiene-1, 3 is an example of this:



In other instances only 1, 2 addition may take place. We shall have occasion to refer to this type of addition quite frequently (p. 293). It should be emphasized that 1, 4 addition may occur with compounds which have conjugated double bonds, but not with dienes which do not contain the system of alternate single and double linkages.

**Methods of Distinguishing the Types of Hydrocarbons.** The only satisfactory proof that a given substance is a hydrocarbon is a quantitative analysis for carbon and hydrogen. If the percentage of these two elements adds up to 100 per cent, one can be

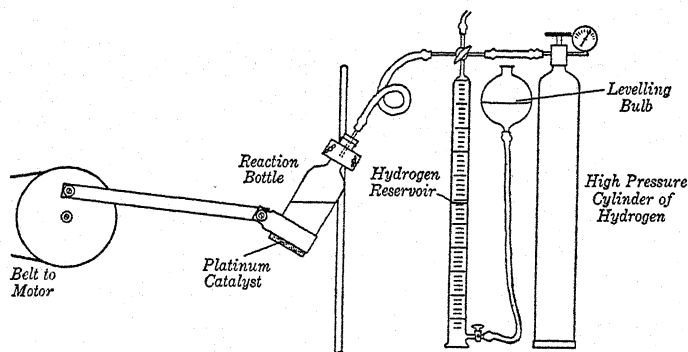


Fig. 12. Apparatus for the quantitative catalytic hydrogenation at room temperature.

sure that a hydrocarbon is at hand. The paraffins and many cycloparaffins (p. 470) are so inert that they are differentiated from the unsaturated hydrocarbons by their failure to react with bromine water, concentrated sulfuric acid, or dilute potassium permanganate solution. The latter oxidizes olefins, diolefins and acetylenes, but is without action on paraffins or cycloparaffins. When potassium permanganate gives up its oxygen, the purple color of the solution is discharged and a brown precipitate of manganese dioxide is formed. **Saturated hydrocarbons** (paraffins and cycloparaffins) may be distinguished from **unsaturated hydrocarbons** by shaking them with the solution and noting whether or not the purple color disappears. Similarly, if the unknown hydrocarbon is shaken with bromine water in the absence of light, the red color will disappear if the material is an olefin or other unsaturated hydrocarbon. **Acetylene hydrocarbons** containing the group  $\text{—C} \equiv \text{CH}$  can be recognized by the formation of a pre-

cipitate of the silver acetylide when treated with ammoniacal silver nitrate.

The determination of the molecular formula of a unknown hydrocarbon (by analysis and molecular weight determination) enables us to decide whether it is in the series  $C_nH_{2n+2}$ ,  $C_nH_{2n}$ ,  $C_nH_{2n-2}$ , etc. It is very useful to determine the degree of unsaturation by a *quantitative catalytic hydrogenation*. This is usually accomplished not at a high temperature but at room temperature using colloidal platinum or palladium as a catalyst. An apparatus for this purpose is shown in Fig. 12. The cycloparaffins are thus clearly distinguished from the olefins, since the latter combine with one mole of hydrogen in the presence of a catalyst while the former do not react. (A further discussion of the hydrogenation of the cycloparaffins is given in Chap. XXVI; some derivatives of cyclopropane  $C_3H_6$  are catalytically hydrogenated very easily.)

### RUBBER

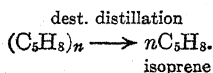
The tremendous increase in the number of automobiles in the last thirty years has not only revolutionized the petroleum industry, but has also produced another important industry, that of the transformation of rubber into rubber tires. Pure rubber or caoutchouc occurs in small globules in the sap of the rubber tree. This tree grows in the jungles of Brazil, and for a long time the Brazilian natives supplied the world with rubber. The primitive method of obtaining rubber consisted in heating the sap over a smoky wood fire, thus evaporating the water and coagulating the caoutchouc.

**Rubber, a Colloid.** If one obtains as pure a sample as possible of crude rubber and examines it in the laboratory, one finds that its analysis corresponds to the formula  $C_5H_8$ . The material dissolves in only a few organic solvents, forming a *colloidal solution*. It is not possible to determine the molecular weight because the substance can not be vaporized without decomposition, and the freezing point and boiling point methods are not applicable to colloidal solutions. The formula  $(C_5H_8)_n$  is often written for it. Like other colloidal substances, caoutchouc solutions are very viscous, and under certain conditions they set to a jelly like substance.

**Vulcanization.** In the process of transforming this crude rubber into commercial articles, it is heated with four or five per cent of sulfur and certain organic compounds which accelerate the reaction between the sulfur and the rubber. This process is called vulcanizing. The finished product is "rubber," as we

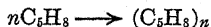
find it in rubber tubing, rubber gloves, and automobile tires. Various coloring materials are often added, and also a certain amount of inert material called fillers. The process is carried out at a temperature somewhat above the boiling point of water; at this temperature rubber is sufficiently plastic to be shaped into various forms. A certain number of rubber goods are also made by dissolving rubber in a solvent and allowing such solutions to evaporate on a suitable surface. This leaves a thin skin of rubber, which may be increased to a desired thickness by repeating the process.

**Isoprene.** A hint as to the structure of the rubber molecule can be obtained by destructively distilling rubber. Under these conditions a certain amount of the low-boiling diolefin, 2-methylbutadiene-1, 3 (isoprene), is formed:

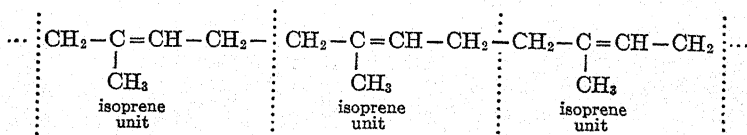


The structure of isoprene was discussed above (p. 73).

**Polymerization of Diolefins.** About the beginning of this century it was shown that isoprene on being treated with catalysts, for example metallic sodium, reverts to a rubber-like solid which was at first thought to be identical with natural rubber. It now seems probable that this is not the case, but the product is a closely related substance. Other diolefins, for example 2, 3-dimethylbutadiene-1, 3,  $\text{CH}_2 = \text{C}(\text{CH}_3)\text{C}(\text{CH}_3) = \text{CH}_2$ , may be converted into rubber-like products. The empirical formula of the product is identical with that of the simple hydrocarbon. For example, the equation for the change of isoprene is:

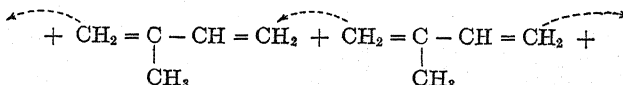


Such a process in which a number of identical molecules join together is called **polymerization**; the product is said to be a **polymer** of the simple substance. The destructive distillation of rubber is the reverse process and is an example of **depolymerization**. We are still uncertain as to how the isoprene molecules are united in the polymer, but it seems probable that they are united in a very long chain thus:



This chain must be imagined as extended until the molecular weight is at least a hundred thousand; at each end of the chain are, perhaps, extra hydrogen atoms instead of the free valences shown.

It is believed that in this polymerization, successive 1, 4 addition of isoprene units occur to yield an elongated chain as formulated above.



**Polymerization of Olefins.** Just as the diolefins polymerize, so too do the homologs of ethylene, although the tendency is much less and the products are of low molecular weight. Generally, high temperatures and pressures and the presence of a phosphoric acid catalyst is necessary for the polymerization of single olefins, although certain inorganic catalysts such as aluminum chloride and boron fluoride can bring about this reaction at low temperatures. The significance of polymerization to the petroleum industry has been discussed (p. 54).

**Synthetic Rubber and Plantation Rubber.** With the sudden demand for rubber caused by the introduction of the automobile, the price of this commodity became very high. In the period 1902-1913, chemists hoped they might be able to produce rubber industrially by polymerizing one of the diolefin hydrocarbons. These polymers, indeed, were produced and from them, by vulcanization, rubber articles such as automobile tires were manufactured. Undoubtedly, if the price of rubber had remained as high as it was at the beginning of this period, synthetic rubber would have become an industrial reality.

The race was won by another group. About 1890, a number of forward-looking men began the cultivation of rubber in plantations in Ceylon and the Straits Settlements, the initial trees having been smuggled from the Brazilian tropics. Figure 13 illustrates the growth of the plantation industry and the parallelism between the production of rubber and the increase in the number of automobiles. When the automobile industry began to grow (1908), wild rubber was the raw material for tires: today it forms less than two per cent of the supply.

About 1913 it became evident that plantation rubber would dominate the market; the price fell, and the chemists abandoned their efforts to synthesize rubber industrially except for special purposes or to meet a special economic situation.

**Artificial Rubber.** The production of artificial rubbers has been undertaken in some countries because of the desire for economic self-sufficiency. In Germany and in Russia a rubber

from butadiene is manufactured. In the latter country butadiene is said to be produced by a high temperature catalytic decomposition of ethyl alcohol in the presence of suitable catalysts. It is said that these rubbers are inferior and more expensive than natural rubber.

Some artificial rubbers possess some properties which are superior in certain respects to those of natural vulcanized rubber.

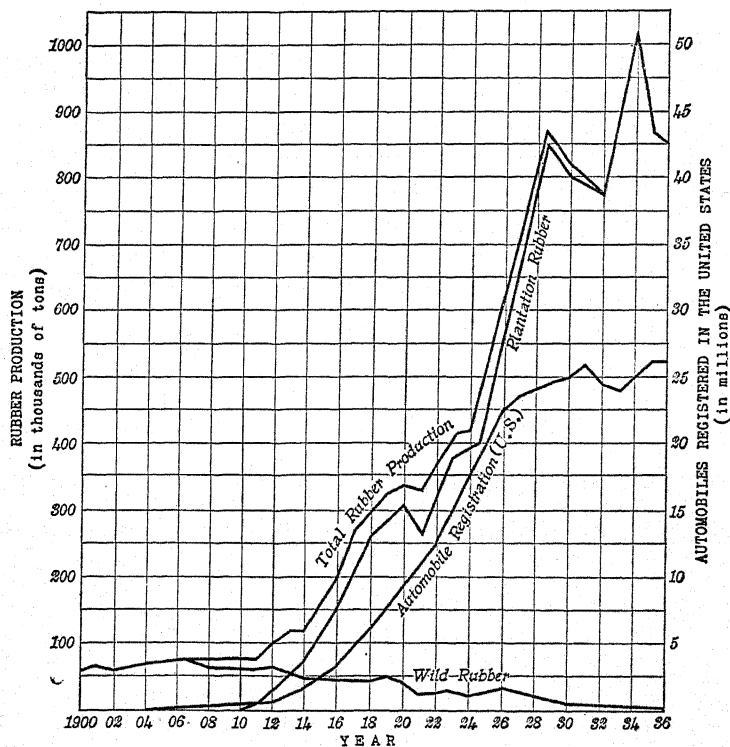
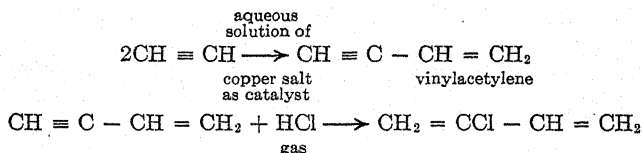


Fig. 13. Chart showing the increase in the world's rubber production and the increase in automobile registration.

One of these rubbers, Duprene, is produced commercially in this country by the polymerization of 2-chlorobutadiene-1, 3,  $\text{CH}_2 = \text{CCl} - \text{CH} = \text{CH}_2$ , known by the trade name of Chloroprene. It is evident that this compound is structurally like isoprene except that it has a chlorine atom in place of a

methyl group. Chloroprene (b.p. 60°) is prepared from the very cheap raw material acetylene:



Chloroprene polymerizes to a rubber-like material more readily than does isoprene; the polymerization can be accomplished at room temperature in a short time. The polymerization may be stopped at a stage in which the product has the properties of natural rubber. This material may be mixed with fillers and coloring materials in the same way as natural rubber. The product is then heated for a short time a little above 100° C. and polymerization occurs further having the properties of vulcanized rubber. This rubber is more resistant to the action of solvents and other chemicals than ordinary vulcanized rubber.

Another artificial rubber now manufactured which has desirable properties is known as "Thiokal rubber." It is prepared by the reaction of ethylene dichloride (p. 58) and sodium polysulfide. Its empirical formula is  $(\text{C}_4\text{H}_8\text{S}_4)_n$ , and very little is known about its structure.

### QUESTIONS AND PROBLEMS

1. Outline the important facts concerning the chemistry of rubber and rubber products including a discussion of the synthesis of rubber.
2. Name two classes of hydrocarbons of the formula  $\text{C}_n\text{H}_{2n-2}$  and give an example of each.
3. Give the reasons for writing the structural formula of ethylene as  $\text{CH}_2 = \text{CH}_2$ .
4. With the aid of equations, show how you could prepare propylene from isopropyl alcohol by several different methods.
5. A certain gas is known to be one of the following: (a) pure ethane; (b) pure acetylene; (c) pure ethylene; (d) pure nitrogen. How could you most readily decide the question?
6. A sample of hexane is contaminated with an unsaturated hydrocarbon. How could you obtain the maximum amount of pure hexane if the impurity were hexylene? If it were butylene?
7. Devise a rough quantitative method of rapidly determining: (a) the percentage of butylene in a mixture of butane and isobutane; (b) the amount of acetylene in a mixture of ethylene and methane.
8. (a) How can one prepare isopropyl bromide from propyl alcohol?  
(b) What alcohol can be readily prepared from isobutylene?

9. A certain compound has the molecular formula  $C_4H_6$ . Write all the possible structural formulas and outline the reactions by which you could decide with which isomer you were dealing.

10. Contrast the chemical properties of ethylene and acetylene pointing out the similarities and dissimilarities.

11. Write balanced equations for the following reactions: (a) symmetrical dimethylethylene and hydrogen bromide; (b) propylene and concentrated sulfuric acid; (c) ethylacetylene and excess hydrogen bromide; (d) *n*-butyl iodide and potassium hydroxide; (e) unsymmetrical diethylethylene and hydrogen chloride.

12. Outline a method of preparation of: (a) diethylacetylene, starting with coke and lime; (b) methyl acetylene from *n*-propyl alcohol; (c) butane from *n*-butyl alcohol; (d) acetylene from ethyl alcohol.

13. Comparing propyl alcohol, isopropyl alcohol, and tertiary butyl alcohol, give the order of reactivity of these in respect to dehydration and their behavior towards halogen acids.

14. Explain what is meant by the statement "Acetylene is an endothermic compound." Explain how the heat of formation of a compound is determined.

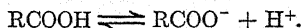
## CHAPTER V

### ORGANIC ACIDS

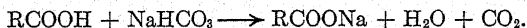
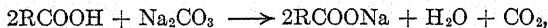
**Formic acid**,  $\text{HCOOH}$ , and **acetic acid**,  $\text{CH}_3\text{COOH}$ , are the first two members of an homologous series known as the **fatty acid series**. The name arises from the fact that two of the higher members — palmitic and stearic acids — are prepared from animal fats. All the acids of the series, except the first, may be represented by the general formula  $\text{RCOOH}$ ; formic acid has a hydrogen atom instead of an alkyl group. The **carboxyl group**

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{OH} \end{array}$  is characteristic of organic acids. We will postpone a discussion of the evidence for its structure until we have learned more about the general nature of the acids of this series.

**The Formation of Salts.** The hydrogen atom of the carboxyl group is acidic; dilute water solutions of organic acids color blue litmus red, evolve hydrogen when acted on by metals, and are neutralized by metallic hydroxides forming salts. In terms of the electrolytic theory of dissociation we write the ionic equilibrium as follows:

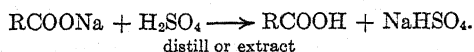


Most organic acids are relatively weak, that is, the degree of the dissociation even in dilute solution is small. For example, in a tenth normal solution of acetic acid, only a few per cent of the molecules are dissociated. However, the organic acids are strong enough to displace the very weak carbonic acid from its salts. Thus, sodium salts may be made from sodium hydroxide, sodium carbonate, or sodium bicarbonate.



**Preparation of Acids from Salts.** The salts of the fatty acids are non-volatile, crystalline solids and are usually soluble in water. The acids are prepared from them by treating with

sulfuric acid. If the acid is sufficiently volatile, it may be distilled. In this case, the dry salt and concentrated sulfuric acid are employed. The higher acids which distill only at high temperatures are more readily obtained from their salts by adding the mineral acid to an aqueous solution and extracting with ether. The organic acid, but not the salt, is soluble in the ether layer. This is an excellent illustration of the use of an immiscible solvent in separating an organic substance (the acid) from an aqueous solution containing inorganic material ( $\text{Na}_2\text{SO}_4$ ,  $\text{H}_2\text{SO}_4$ ). The ether is easily removed by evaporation.



**Physical Properties.** There is a gradual change in boiling point and solubility in water as we proceed from one member of the homologous series to the next higher straight chain com-

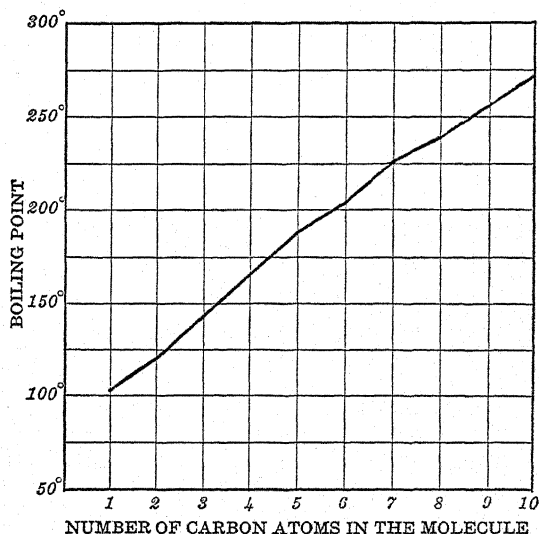


Fig. 14. The boiling points of the straight chain fatty acids,  $\text{HCOOH}$  to  $\text{C}_9\text{H}_{19}\text{COOH}$ .

pound. This is illustrated in Fig. 14 in which the curve shows the increase in boiling point with each increment of  $\text{CH}_2$ . The acids above butyric are only slightly soluble in water, and the solubility decreases as the hydrocarbon portions of the molecule become more predominant with the increase in the number of

carbon atoms. The acids are all very soluble in alcohol, ether, benzene, and chloroform and even the lower members may be extracted from their water solutions by the last three solvents.

Some of the physical properties of the series are given below:

NAME	FORMULA	BOILING POINT	MELTING POINT	DENSITY AT 20°	SOLUBILITY GRAMS PER 100 GRAMS OF WATER AT 20°
Formic acid	HCOOH	101°	8°	1.220	miscible in all proportions
Acetic acid	CH <sub>3</sub> COOH	118°	17°	1.049	
Propionic acid	CH <sub>3</sub> CH <sub>2</sub> COOH	141°	-22°	0.992	
<i>n</i> -Butyric acid	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	164°	-8°	0.959	
Isobutyric acid	(CH <sub>3</sub> ) <sub>2</sub> CHCOOH	154°	-47°	0.949	
<i>n</i> -Valeric	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	187°	-18°	0.942	4
<i>n</i> -Caproic	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	202°	-1.5°	0.929	less than 1
<i>n</i> -Heptoic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> COOH	223°	-10°	0.918	less than 1
Caprylic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> COOH	237°	16°	0.914	less than 1
<i>n</i> -Nonylic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> COOH	253°	12.5°		Practically insoluble
Capric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> COOH	268°	31°		
Undecylic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> COOH		28.5°		
Lauric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> COOH		43°		
Tridecyllic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> COOH		42.5°		
Myristic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>12</sub> COOH		53.8°		
Pentadecylic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>13</sub> COOH		53°		
Palmitic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> COOH		64°		
Margaric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>15</sub> COOH		61°		
Stearic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> COOH		69°		

It will be noted that the melting points of the straight chain acids show no regular increase but vary up and down; the melting point of the acids containing an even number of carbon atoms is higher than the preceding one in the series. The straight chain acid with a total of nine carbon atoms melts at 12.5°, and all those above this are solid at room temperature. The odor of the acids above propionic is very disagreeable unless they are so non-volatile as to be practically odorless. Rancid butter owes its disagreeable smell to butyric acid.

**Dissociation Constants.** Those who are familiar with the quantitative aspects of the theory of electrolytic dissociation will recall that the strength of acids may be expressed in terms of a dissociation constant  $K_A$  which is defined as follows:

$$K_A = \text{conc. of hydrogen ion} \times \left( \frac{\text{conc. of acid ion}}{\text{conc. of undissoc. acid}} \right)$$

It is evident that when the quotient inside the parenthesis has a value of one, the value of  $K_A$  is equal to the concentration of the hydrogen ion. This condition is easily realized in the case of weak acids by preparing a solution which

Name of Acid	$K_A$
Hydrochloric Acid	Too Strong to Measure
Sulfuric Acid	
Dichloroacetic Acid	$5 \times 10^{-2}$
Chloroacetic Acid	$1.5 \times 10^{-3}$
Formic Acid	$2.1 \times 10^{-4}$
Acetic Acid	$1.8 \times 10^{-5}$
Carbonic Acid (First Hydrogen)	$1 \times 10^{-7}$
Phenol	$1.7 \times 10^{-10}$
Carbonic Acid (Second Hydrogen)	$5 \times 10^{-11}$

contains one mole of the acid and one mole of a soluble salt of the acid. Since the free acid is only very slightly dissociated, the concentration of the undissociated acid is practically the same as the total concentration. The salt, on the other hand, is completely ionized and the concentration of the acid ion is therefore equal to the total concentration of the salt. Therefore, one may visualize the dissociation constant of a weak acid by thinking of it as being equal to the acidity (the hydrogen ion concentration) of a mixture of the acid and its soluble salt in equal molar amounts. The dissociation constants of some of the fatty acids are as follows:

$$\text{Formic, } K_A = 2.14 \times 10^{-4}$$

$$\text{Acetic, } K_A = 1.86 \times 10^{-5}$$

$$n\text{-Butyric, } K_A = 1.6 \times 10^{-5}$$

Fig. 15. The relative strengths of some common acids. The strongest acids are at the top; each unit of the scale corresponds to a ten-fold change in the acid dissociation constant.

$1 \times 10^{-7}$  and  $5 \times 10^{-11}$ , respectively. The diagram in Fig. 15 shows graphically the relative acidities of some common acids; several acids are included which will be considered later (phenol p. 352, chloroacetic acid p. 100).

It will be recalled that the hydrogen ion concentration of pure water =  $1 \times 10^{-7}$ . The dissociation constants of the first and second hydrogens of carbonic acid are about

**Nomenclature.** A great many of the fatty acids having a straight chain are found in nature, and were isolated before chemical nomenclature had been put on a rational basis; for this reason they have acquired trivial names. In a systematic fashion, acids may be named as derivatives of acetic acid or by the Geneva system. The former method is illustrated by the following example, trimethylacetic acid,  $(\text{CH}_3)_3\text{CCOOH}$ . This is a convenient method for relatively simple acids.

In the Geneva system, the acid is named according to the longest chain of carbon atoms which it contains, *counting the carbon of the carboxyl group*. The suffix *-oic* is then added to the name of the paraffin hydrocarbon corresponding to this chain;

branches are named and numbered as in the case of the hydrocarbons. The numbering is always started *on* the carboxyl group. The following examples will make this method clear: pentanoic acid,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ ;  $\text{CH}_3\text{CHCH}_2\text{COOH}$ , 3-methyl-

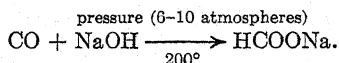


butanoic acid.

### FORMIC ACID

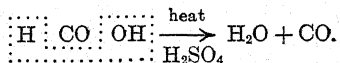
The first member of the homologous series occurs in nature, particularly in nettles and ants (*formica*). The irritating effect of ant stings is due in part to formic acid. The early chemists prepared formic acid by distilling red ants. The acid is a colorless liquid boiling at  $101^\circ$ ; it can not be freed from water by simple distillation. The anhydrous acid is prepared by distillation from anhydrous copper sulfate under diminished pressure.

**Preparation.** Formic acid is prepared from sodium formate, which in turn is prepared from the simple substances carbon monoxide (from water gas) and sodium hydroxide.



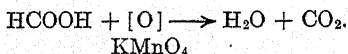
To prepare the acid, the salt is heated with the calculated quantity of sulfuric acid.

**Unique Reactions of Formic Acid.** If sodium formate is heated with an excess of sulfuric acid, the formic acid decomposes according to the following equation:

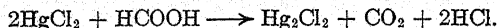


This reaction is one of those peculiar to formic acid. It is evident that such a reaction is connected with the fact that in formic acid a hydrogen atom and not an alkyl group is directly attached to the carboxyl group.

Formic acid also differs from the other acids of this series in being relatively easily oxidized. For example, it is readily oxidized by potassium permanganate,



Formic acid will reduce mercuric salts,

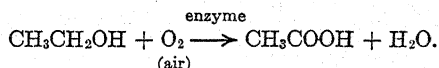


**Uses of Formic Acid.** Formic acid is used for the preparation of certain special compounds in the organic laboratory and in industry. It is also used in connection with the application of dyestuffs and the treatment of textiles, and in cases where an acid reducing agent is desired.

#### ACETIC ACID

The most important of all the simple acids is acetic acid. One meets with it commonly in two forms — concentrated acetic acid (often called *glacial acetic acid*) and a dilute solution of the acid known as *vinegar*. It is interesting that two entirely different processes are used for preparing acetic acid according to whether a very dilute solution (vinegar) is wanted or at least a 50 per cent solution of the acid.

**Preparation of Vinegar.** Vinegar is still prepared by the ancient process in which fruit juices are allowed to undergo first the alcoholic fermentation, and then an acetic acid fermentation. A dilute solution of alcohol is produced by the alcoholic fermentation of wine or cider. In the presence of a certain microorganism *bacterium aceti* (often called "mother of vinegar"), oxygen from the air oxidizes the alcohol to acetic acid. This change is undoubtedly brought about by an enzyme present in the organism.



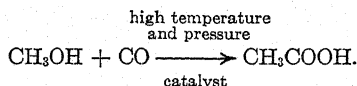
As originally carried out the process is slow; the action only takes place as fast as the oxygen is dissolved at the surface of the liquid standing in the vinegar barrel. In the so-called quick vinegar process a dilute solution of alcohol, usually made from starch (p. 314), is used. It is trickled over a mass of beech wood shavings contained in a tall vat; these have previously been soaked in vinegar and are covered with "mother of vinegar." This process proceeds much more rapidly since an enormous surface is exposed to the air which circulates through the vat. By allowing a solution to trickle a few times through the apparatus, the oxidation is complete. The product contains four to six per cent of acetic acid.

**Preparation of Acetic Acid.** For chemical purposes a concentrated acetic acid is required. This is not prepared by concentrating a crude vinegar, because the evaporation of so much water is an expensive operation. At one time the more concentrated solutions of acetic acid were obtained solely from the by-products

of the destructive distillation of wood (p. 15). It will be recalled that in this process acetic acid is present in the distillate in a concentration of about 8 per cent. The acetic acid is separated from the aqueous mixture by a process of continuous extraction using ethyl or isopropyl ether as the solvent.

The most important commercial method of preparing pure acetic acid starts with acetylene. This synthesis will be discussed later (p. 145).

Methyl alcohol and carbon monoxide under high pressure and temperature in the presence of a suitable catalyst will combine to form acetic acid. This reaction is now used to some extent in the manufacture of acetic acid.

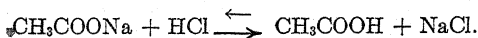


**Physical Properties.** Pure anhydrous acetic acid is a solid which melts at 16.6°; it is hygroscopic. The liquid boils at 118°. It is miscible in all proportions with water, alcohol, ether, and most organic solvents. It is an excellent solvent for many organic solids and some inorganic salts. The specific gravity of the pure liquid is 1.055 but an 80 per cent solution of it in water has the higher value of 1.075; more dilute solutions have lower densities approaching 1.00 as the solution becomes very dilute.

**Uses of Acetic Acid.** Since acetic acid is a relatively cheap substance which has been produced for many years, it has found a great variety of uses. It is the starting point in the manufacture of a whole host of other organic compounds, some of which are of great technical importance. This is particularly true of the acetic esters of the simple alcohols. Dilute acetic acid is not injurious to textiles and is relatively non-corrosive to the skin; it is therefore often used in the industries for purposes for which mineral acids (hydrochloric or sulfuric) would be too powerful and corrosive. Glacial acetic acid is a good solvent and is used in the laboratory and to some extent in industry for this purpose. The industrial importance of acetic acid is illustrated by the fact that the equivalent of 200 million pounds of glacial acetic acid was produced during 1937.

Sodium acetate,  $\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$ , and potassium acetate,  $\text{CH}_3\text{COOK}$  are colorless, crystalline solids. Anhydrous sodium acetate is prepared by

dehydrating the hydrate at a moderate temperature. These compounds are frequently used in organic reactions, usually to convert a mineral acid into the weaker acetic acid:



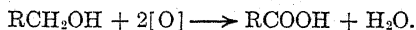
**Lead acetate**,  $(\text{CH}_3\text{COO})_2\text{Pb}$ , called "sugar of lead" because of its sweet taste, is very poisonous. Its aqueous solution is used in biochemistry for precipitating compounds which form insoluble lead salts. It is used as a mordant in the dyeing of cotton cloth as are also the acetates of aluminum,  $(\text{CH}_3\text{COO})_3\text{Al}$ , and iron,  $(\text{CH}_3\text{COO})_3\text{Fe}$ . The latter is a brown red solid which gives a wine red solution. A mixture of copper acetate and copper arsenite is a bright green powder known as **Paris green**; it is used as an insecticide.

**Calcium propionate**  $(\text{CH}_3\text{CH}_2\text{COO})_2\text{Ca}$  has recently come into use as an inhibitor for the growth of molds and ropes in bread and other foods.

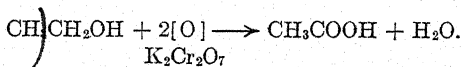
### GENERAL METHODS OF PREPARING ACIDS

As we have seen, the two important lower members of the fatty acid series are prepared industrially by special methods, or from special sources. When we wish to prepare any of the other fatty acids in the laboratory, we use an alcohol as our starting point.

**Oxidation of a Primary Alcohol.** If we have a primary alcohol with the same number of carbon atoms, the problem is easy. The oxidation of a primary alcohol yields an acid with the same number of carbon atoms:



An illustration of this is the oxidation of ethyl alcohol by air in the presence of "mother of vinegar." In the laboratory a mixture of potassium dichromate and sulfuric acid is often employed as the oxidizing agent. Under certain conditions an intermediate product, — an aldehyde (Chap. VI), — may be isolated, but if the process is so arranged that this compound remains in contact with the oxidizing agent it is further oxidized to the acid. The simple organic acids themselves are not readily oxidized, so that there is little danger of carrying the process too far:

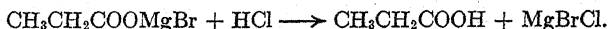
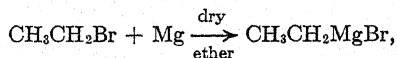


It will be noted that  $\text{RCH}_2\text{OH}$  is a general formula for any primary alcohol and  $\text{RCOOH}$ , for the corresponding acid. In the

case of formic acid, which has the formula  $\text{HCOOH}$ , the corresponding alcohol is  $\text{CH}_3\text{OH}$ .

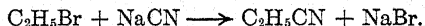
**Acids from Lower Alcohols.** If we have the problem of preparing an acid with one more carbon atom than the alcohol at hand, a simple oxidation will not avail. There are two ways of accomplishing this synthesis, however. Both start with the alkyl halide  $\text{RX}$  and yield the same acid  $\text{RCOOH}$ . They are illustrated below by the synthesis of propionic acid from ethyl bromide.

- (1) **Grignard Synthesis of Acids.** In this process dry carbon dioxide is passed into the ethereal solution of the Grignard reagent. After a few hours the mixture is treated with dilute hydrochloric or sulfuric acid; the magnesium salts of the inorganic acids stay in the water. (These salts are written as  $\text{MgBrCl}$  below; this is equivalent to a mixture of  $\text{MgBr}_2$  and  $\text{MgCl}_2$ ).

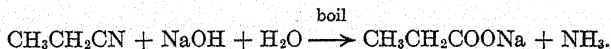


The organic acid is extracted with ether and is obtained by evaporating this solvent. This process is a good laboratory method of preparing many acids and has been widely employed since the discovery of the Grignard reaction.

- (2) **Nitrile Synthesis of Acids.** The older process of preparing acids involves the preparation of a nitrile,  $\text{RCN}$ . This substance has the carbon atom of the cyanide group directly bound to the alkyl group. It is an organic cyanide and may be regarded as an ester of hydrocyanic acid. The nitriles are formed by boiling an alcoholic solution of the alkyl halide with sodium cyanide (p. 26).

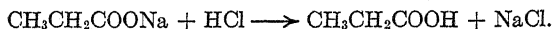


The nitriles are hydrolyzed on boiling with dilute alkalis:



The product is the sodium salt; from the water solution

of the salt the free acid may be prepared by acidification with a mineral acid and extraction with ether:



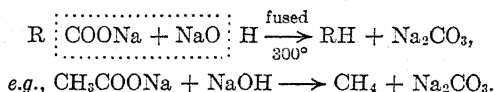
The hydrolysis of nitriles to acids may also be accomplished with strong mineral acids:



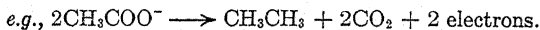
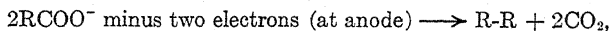
#### SOME GENERAL REACTIONS OF ACIDS

The acidic reaction of the carboxyl group is perhaps the most characteristic property of organic acids. Certain other reactions, however, are important. They are illustrated by the following general equations, where  $\text{RCOOH}$  stands for acetic acid or a higher homolog:

(1) *Formation of paraffin hydrocarbon RH:*



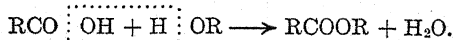
(2) *Formation of hydrocarbon R-R by electrolysis of sodium salt:*



(3) *Replacement of OH by halogen; formation of acid chlorides:*



(4) *Replacement of OH by OR group; formation of esters:*

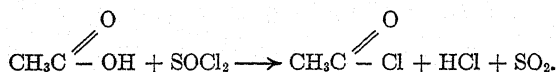


The first two reactions require no particular comment; they have been frequently used for the preparation of hydrocarbons. The second reaction gives very low yields in the case of the higher fatty acids and its use is thereby limited. The last two reactions are the most important. We shall consider the acid chlorides first and then turn to the esters.

#### ACID CHLORIDES

When an acid is treated with phosphorus trichloride ( $\text{PCl}_3$ ), the OH group of the carboxyl group is replaced by chlorine as illustrated by equation 3 above. This reaction is exactly like a

reaction of alcohols (p. 6); some hydrogen chloride is evolved due to a secondary reaction between the acid chloride and phosphorous acid. Phosphorus pentachloride and thionyl chloride ( $\text{SOCl}_2$ ) are also used in replacing the OH group of acids. The action of the latter is illustrated below:

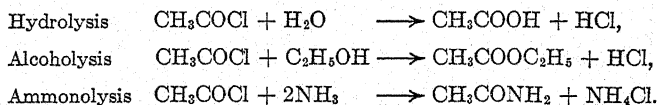


An acid chloride is also called an **acyl chloride**. It has the general formula  $\text{RCOCl}$ , and is named by slightly changing the name of the acid; thus, acet-yl chloride and propion-yl chloride. Formyl chloride,  $\text{HCOCl}$ , is unknown; attempts to prepare it yield only hydrogen chloride and carbon monoxide. Acid bromides and acid iodides are known but are of no importance. The boiling points of the lower acyl chlorides are given below:

NAME	FORMULA	BOILING POINT
Acetyl chloride	$\text{CH}_3\text{COCl}$	52°
Propionyl chloride	$\text{CH}_3\text{CH}_2\text{COCl}$	80°
Butyryl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{COCl}$	102°

These substances are all very irritating to the mucous membrane, and fume in moist air.

**Reactions of Acid Chlorides.** Acyl chlorides are much more reactive than alkyl halides. Acetyl chloride reacts violently with water, alcohol, and ammonia at room temperature:



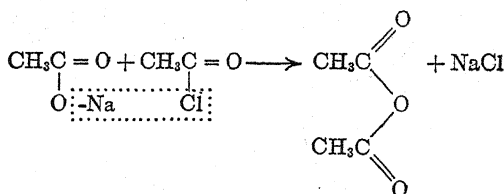
The product of the second reaction is an **ester**; the substance formed in the last reaction is an **amide**. These reactions show that the acid chlorides are useful in preparing other compounds.

The characteristic reactions of acyl chlorides are all replacement reactions in which the halogen atom is replaced by a group of atoms. With the acid chlorides of the simpler acids these reactions occur very rapidly at room temperature, in fact often with almost explosive violence. This behavior of the *acyl* chlorides is in marked contrast to that of the alkyl halides such as ethyl chloride. The alkyl chlorides can be boiled with water and alcohol

without any appreciable reaction; in order to replace the halogen with hydroxyl in these compounds, silver hydroxide or an alkali is necessary. The speed of the reaction between an acid chloride and an alcohol depends on the structure of both. Acetyl chloride is more rapid in its reactions than the higher homologs, and primary alcohols interact faster with a given acid chloride than do secondary or tertiary. In this reaction it will be noted that the hydrogen atom of the alcohol is being replaced just as in the case of the formation of alcoholates with metallic sodium, and just as in this case, the primary alcohols are the most reactive, secondary next, and tertiary least. When it is a matter of replacing the *hydroxyl* group of the alcohols, however, as in the formation of alkyl halides, the situation is just reversed, and the tertiary alcohols are the most rapid in their action (p. 24).

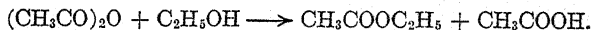
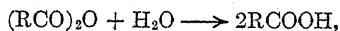
### ACID ANHYDRIDES

When anhydrous sodium acetate and acetyl chloride are heated together, a reaction takes place and **acetic anhydride**,  $(\text{CH}_3\text{CO})_2\text{O}$  is formed:



This compound is a representative of the acid anhydrides

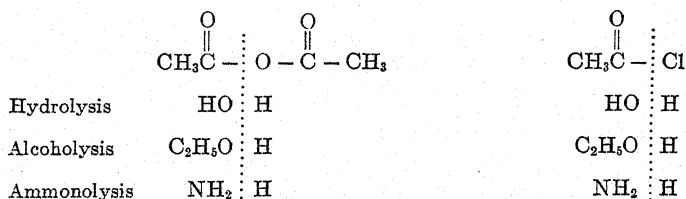
$\text{RC} \begin{array}{c} \nearrow \text{O} \\ \searrow \text{O} \end{array} \text{C} \begin{array}{c} \nearrow \text{O} \\ \searrow \text{O} \end{array} \text{R}$  or  $(\text{RCO})_2\text{O}$ . They are formally related to acids as the ethers are to alcohols. There is little resemblance in properties, however, between the two classes. The anhydride of formic acid is unknown; all attempts to prepare it yield carbon monoxide. As the name indicates, the anhydrides react with water, regenerating acids; they also react with alcohols forming esters.



**Acetic Anhydride.** Acetic anhydride is prepared in the laboratory from sodium acetate and acetyl chloride, and industrially by the action of sulfur chloride ( $\text{S}_2\text{Cl}_2$ ) on acetic acid or sodium acetate. It is a liquid boiling at  $140^\circ$ ; it has a very irritating odor. Its importance depends on the fact that it reacts with many

substances forming acetyl derivatives, that is, compounds containing the acetyl group  $\text{CH}_3\text{CO}-$ . Large quantities of acetic anhydride are manufactured for the production of cellulose acetate, one of the artificial silks now widely used (p. 321). During 1935 over 116 million pounds of acetic anhydride was produced.

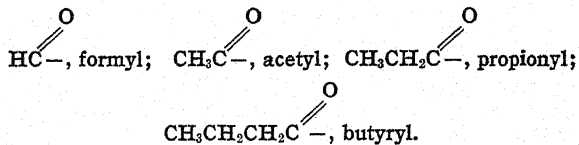
**Acetylating Agents.** Acetyl chloride and acetic anhydride are spoken of as acetylating agents because they will react with many substances having an active hydrogen and form acetyl derivatives. This is illustrated in the case of water, alcohol, and ammonia by the following diagrams:



#### ACYL GROUPS AND ALKYL GROUPS

The acyl group  $\text{RCO}-$  may be regarded as the hypothetical group formed from an acid by removal of the  $\text{OH}$  group. The acyl groups should not be confused with the acid ion  $\text{RCOO}^-$ .

For example, the acetyl group  $\text{CH}_3\overset{\text{O}}{\parallel}\text{C}-$  is quite different from the acetate ion  $\text{CH}_3\text{COO}^-$ . The names of the common acyl groups are:



The acid chlorides and anhydrides are named with reference to the acyl group which they contain. The formyl group is met with only in esters since the acid chloride and anhydride are unknown.

The following table may serve as a general review of some of the types of compounds thus far studied. The contrast between the *acyl* and corresponding *alkyl* compounds should be carefully studied; they bear a formal resemblance to each other, but their chemical and physical properties are very different.

COMPOUNDS HAVING AN ALKYL GROUP		COMPOUNDS HAVING AN ACYL GROUP	
CLASS NAME	GENERAL FORMULA	CLASS NAME	GENERAL FORMULA
Alcohol	ROH	Acid	$\begin{array}{c} \text{O} \\ \parallel \\ \text{RC}-\text{OH} \end{array}$
Alkyl chloride	RCI	Acyl chloride	$\begin{array}{c} \text{O} \\ \parallel \\ \text{RC}-\text{Cl} \end{array}$
Ether	ROR	Acid anhydride	$\begin{array}{c} \text{O} \qquad \text{O} \\ \parallel \qquad \parallel \\ \text{RC}-\text{O}-\text{C}-\text{R} \end{array}$

## ESTERS OF ORGANIC ACIDS

The esters of organic acids except formic have the general

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{RC}-\text{OR}' \end{array}$$
 (RCOOR') where R and R' may be the same or different alkyl groups; the esters of formic acid have the general formula HCOOR. There is, therefore, an homologous series for each acid, the alkyl groups becoming increasingly larger. Thus, we have methyl formate, HCOOCH<sub>3</sub>; ethyl formate, HCOOC<sub>2</sub>H<sub>5</sub>; propyl formate, HCOOC<sub>3</sub>H<sub>7</sub> (two isomers) etc. Similar series may be written with acetic acid, propionic acid, and all the other fatty acids.

In the following table are listed some of the commoner esters which can be prepared from the alcohols and acids already considered. They are all liquids which float on water.

The esters have a very pleasant, fruity odor, each different from that of the others. It is particularly interesting that although butyric and valeric acids have very disagreeable odors, their esters are sweet-smelling substances. The characteristic fragrance of many fruits and flowers is due to the presence of various esters. Thus, amyl acetate, CH<sub>3</sub>COOC<sub>5</sub>H<sub>11</sub>, has a pear-like odor and the odor of methyl butyrate, C<sub>3</sub>H<sub>7</sub>COOCH<sub>3</sub>, is reminiscent of pineapple.

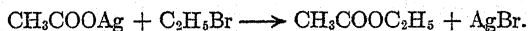
## SOME COMMON ESTERS

NAME	FORMULA	BOILING POINT
Methyl formate	$\text{HCOOCH}_3$	32°
Ethyl formate	$\text{HCOOCH}_2\text{CH}_3$	54°
Methyl acetate	$\text{CH}_3\text{COOCH}_3$	57°
Ethyl acetate	$\text{CH}_3\text{COOCH}_2\text{CH}_3$	77°
<i>n</i> -Butyl acetate	$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	127°
<i>n</i> -Amyl acetate	$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	148°
Isoamyl acetate	$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	143°
Methyl propionate	$\text{CH}_3\text{CH}_2\text{COOCH}_3$	80°
Ethyl propionate	$\text{CH}_3\text{CH}_2\text{COOCH}_2\text{CH}_3$	99°

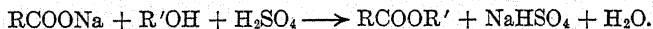
A number of the simple esters are manufactured for use in preparing artificial perfumes and flavors. The most important use of esters is as solvents, especially in the manufacture of quick-drying automobile lacquers (p. 319).

The fats and oils which occur in animals and plants are esters of an alcohol with three hydroxyl groups and acids of high molecular weight. They are of great importance, not only as food, but as the raw material used in manufacturing soap, candle stock, and glycerine (Chap. IX).

**Preparation of Esters.** Esters may be prepared by four different methods: (1) direct esterification; (2) the action of an acid chloride on an alcohol (p. 91); (3) the action of an acid anhydride on an alcohol (p. 92); (4) the action of an alkyl halide on the silver salt of an acid:



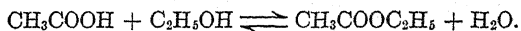
The first method is by far the most important. The alcohol to be esterified is heated with the organic acid and a little mineral acid (hydrochloric or sulfuric), or else with equivalent quantities of sulfuric acid and the sodium salt of the organic acid. In the latter case, the sulfuric acid fulfils two functions: that of liberating the organic acid from the salt and that of catalyzing the esterification:



The ester is usually separated by distillation from the reaction mixture and any unchanged acid or alcohol removed by washing with sodium carbonate and then with calcium chloride solution.

**Esterification and Hydrolysis.** The interaction of an alcohol and acid does not go to completion as do most organic reactions. If we start with one mole of acetic acid (60 g.) and one mole of ethyl alcohol (46 g.), we find that, try as we will, we can not get a reaction mixture containing more than about 66 per cent of one mole of ethyl acetate. On the other hand, if we were to start with ethyl acetate and heat it with one mole of water for a long time, we would find that the hydrolysis (p. 29) apparently stopped when the mixture contained about 66 per cent of unchanged ester. Thus, whether we start with alcohol and acid or with water and ester, *the final composition of the reaction mixture is the same*. This state of affairs is typical of a reversible reaction; the final reaction mixture of constant composition (in this case about 66 per cent ester) is said to be an **equilibrium mixture**.

**Reversible Reactions.** A reversible reaction is usually written with a double arrow, thus:



A study of reversible reactions has shown that at equilibrium the two reactions (left to right and right to left of the equation) are proceeding at the same rate; for this reason the composition of the final reaction mixture is constant.

**Rate of Reactions.** The reversible organic reactions differ from those usually met with in inorganic chemistry (ionic reactions) in that it takes time for most organic reactions to reach equilibrium. Thus, if we mix pure ethyl alcohol and acetic acid, it will be a matter of days before the maximum amount of ethyl acetate is formed. The rate of a reaction may be accelerated by three methods: (1) increasing the temperature; (2) increasing the concentration of the reactants; (3) using a catalyst. This applies to both the reactions which run to completion (irreversible reactions), and to reversible reactions. Thus, if we wish to hasten the preparation of ethyl acetate, we add a few drops of sulfuric acid as a catalyst, and boil the mixture. Acids and bases act as catalysts for a great many different organic reactions, as we have already seen. In connection with these facts, the esterification of formic acid deserves mention. Since it is relatively a strong acid, catalysts need not be added as it itself can fulfill this function.

While the rate of attaining equilibrium is greatly affected by

the presence of catalysts, the composition of the equilibrium mixture is not changed by their presence. Hence we may accelerate the process of esterification by using a catalyst, but we can not make the reaction go to completion. Increasing the temperature always increases the rate of a reaction, but it may influence the composition of the equilibrium mixture in either direction. In the case of esterification, it happens that the effect of temperature on the position of the equilibrium is very slight. About 66 per cent of ester is obtained at 60° or at 200° (in a sealed tube).

**The Composition of the Equilibrium.** The composition of an equilibrium mixture is approximately expressed by what is often called the *mass law*. This is given by the following equation in which the symbols [ester], [H<sub>2</sub>O], etc., refer to concentrations expressed as moles per liter, or better as mole fractions:

$$\frac{[\text{Ester}] \times [\text{H}_2\text{O}]}{[\text{Alcohol}] \times [\text{Acid}]} = K \text{ (the equilibrium constant).}$$

For example, in the case of ethyl acetate, experiments show that the equilibrium mixture contains about 0.6 mole of ester, if we start with one mole of acid and one of alcohol (a total of 2 moles).

Therefore, the mole fraction of ester is  $\frac{0.6}{2} = 0.3$  and of water the same (for each molecule of ester formed, one of water is also formed). The concentrations of alcohol and acid are  $\frac{0.4}{2} = 0.2$  each. These numbers substituted in the equation give us

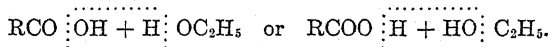
$$\frac{0.3 \times 0.3}{0.2 \times 0.2} = 2.25 = K.$$

Experiment shows that whatever relative amounts of acetic acid and ethyl alcohol are employed, the composition of the equilibrium mixture is such that K has *approximately* this value.

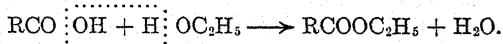
**Practical Applications of the Mass Law.** It is an easy matter to calculate the composition of an equilibrium mixture if we know the value of K and the relative amounts of alcohol and acid at the start. Without going through the calculations, it is evident from an inspection of the mass law equation that if we use a large excess of alcohol, the yield of ester per mole of acid will be increased. For this reason, if we wish to prepare the ethyl ester of an expensive acid we use a considerable excess of the alcohol.

It is also evident that if we remove a certain amount of one of the products (water or ester), a further amount will be formed so that the composition of the mixture will conform to the mass law expression. This can be realized very often in practice and is sometimes referred to as "upsetting the equilibrium." For example, if the alcohol, ester, and acid boil much higher than water, it is often possible to distill off the latter from the reaction mixture. This is also accomplished by making use of an azeotropic mixture (p. 17). Some solvent such as benzene is added to the acid and alcohol. On distillation at a relatively low temperature, a mixture of water and benzene is separated from the reaction mixture. In this way the yield of the process may be much greater than otherwise would be possible. It should be noted that these methods are only effective if they are carried out under such conditions (temperature and catalyst) that the rate of the reactions is rapid and more product will be rapidly formed if some is removed.

**Mechanism of Esterification and Hydrolysis.** It is obvious that two schematic representations of the esterification reaction may be written depending upon whether the acid or the alcohol loses an hydroxyl group. The water formed during esterification must arise from one of the following paths:



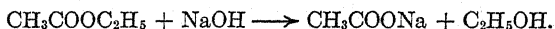
The question as to which mechanism is correct has been definitely settled by esterifying an organic acid with methyl alcohol containing an abnormal amount of the heavy oxygen isotope (atomic weight 18). The water obtained from this experiment had the normal density showing that the oxygen atoms in the water were a mixture of the isotopes in the usual normal manner. This in turn proved that the oxygen in the water did not originate from the alcohol but rather from the acid; thus:



This is an illustration of how it is sometimes possible to establish the mechanism of a reaction by "tagging" one of the atoms, as it were, by employing an isotope.

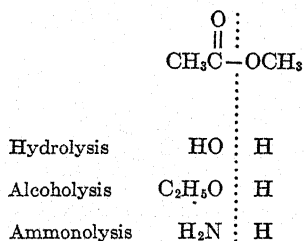
**Saponification of Esters.** If we heat an ester with water, the hydrolysis is slow unless an acid or base is present to accelerate the process. In the former case, the reaction soon reaches an equilibrium, and only about a third of the ester is hydrolyzed. If an equivalent amount of base is employed, however, the acid formed is neutralized and hence removed from the equilibrium.

The process thus goes to completion. It is a special instance of hydrolysis and is called *saponification*:

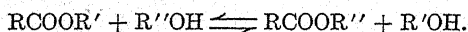


**Rates of Esterification and Hydrolysis.** It has been found that the rate of formation of esters (under given conditions) depends on the structure of the acid and alcohol. Primary alcohols react most rapidly, tertiary least rapidly, with secondary in between. It will be noted this is the *reverse* of the order met with in alkyl halide formation; this is explained by the fact that in the one case the hydroxyl of the alcohol is necessarily involved and in the other the hydroxyl of the acid is eliminated (as demonstrated above). It is often difficult to esterify tertiary alcohols by the direct method. Acids of the general formula  $\text{R}_3\text{C} - \text{COOH}$  are also difficult to esterify directly. In general, branching the chain next to the carboxyl group causes the acid to esterify more slowly. Branching the chain of the alcohol has the same effect.

**Reactions of Esters with Alcohols and Ammonia.** Like the acid chlorides and acid anhydrides, the esters can undergo alcoholysis and ammonolysis as well as hydrolysis. This is illustrated in the case of methyl acetate by the following diagram:

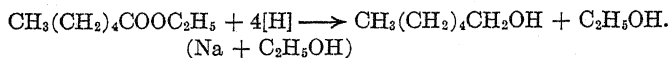


The reaction with ammonia is a method of preparing amides (p. 149). The alcoholysis reaction is also known as *ester interchange*. It takes place extremely slowly in the absence of a catalyst but very rapidly if a trace of sodium alcoholate is added to the mixture. The reaction does not go to practical completion unless there is a very large excess of one of the alcohols, or unless some provision is made for removing one of the products.

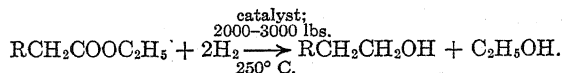


**Reduction of Esters to Alcohols.** Esters are reduced to primary alcohols in good yields by the action of sodium and alcohol or by sodium and moist ether. The following equation for the prepara-

tion of *n*-hexyl alcohol from the ethyl ester of *n*-caproic acid illustrates the method:



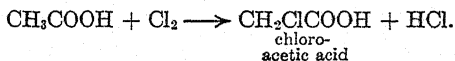
Esters may also be reduced catalytically with excellent results. The ester is shaken with hydrogen at elevated temperature and high pressures in the presence of a mixed catalyst of copper and chromium oxide (copper chromite).



This process is convenient; industrially it is preferable to the sodium reduction because of the lower cost and the hazards which attend the handling of sodium. Because of this method a number of higher alcohols, which were once rare, are now manufactured on a large scale (p. 18).

**Other Reactions of Acids and Their Derivatives.** It will be noticed that in all the reactions previously discussed in this chapter, only the carboxyl group is involved, — the alkyl residue has not been modified. We shall now consider a reaction in which the hydrocarbon portion of the molecule is altered.

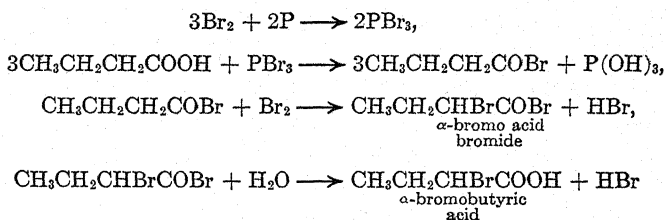
**Halogenation.** The organic acids react with chlorine at elevated temperatures. The reaction is catalyzed by sunlight or by a trace of iodine. Unlike the hydrocarbons (p. 49) the reaction can be controlled and a pure product can be obtained. A hydrogen atom on the carbon next to the carboxyl group (called the alpha carbon atom) is replaced. With acetic acid, chloroacetic acid is formed:



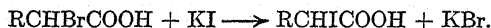
If there is no hydrogen in alpha position as in (CH<sub>3</sub>)<sub>3</sub>CCOOH, this reaction obviously can not occur.

The same reaction occurs with esters, anhydrides, and acyl chloride and bromides. For some reason chlorination and bromination of these substances take place more rapidly than with the corresponding acids. A convenient method of accomplishing the bromination of fatty acids which makes use of this fact is known as the **Hell-Volhard-Zelinsky method**. It consists of pre-

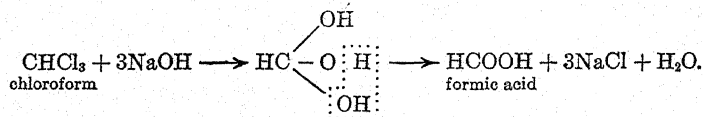
paring the acid bromide and carrying out the bromination in one step. Liquid bromine is dropped onto a mixture of the acid and red phosphorus. The phosphorus tribromide which is first formed reacts with the acid substituting a bromine atom for the hydroxyl group and producing an acid bromide, which is in turn brominated. Finally the reaction mixture is treated with water or alcohol, the acid bromide then reacts in the same way as an acid chloride (p. 91). The reactive bromine atom is substituted by hydroxyl or ethoxyl and the brominated acid or ester is obtained which is separated and purified by distillation. Even if an excess of bromine is used, the reaction stops after the introduction of one bromine atom in the alpha position. Further bromination requires a high temperature and special conditions. The reactions may be summarized using butyric acid:



Since iodine does not react with acids or their derivatives in this manner, the introduction of an iodo atom is accomplished indirectly. Alpha iodo acids result readily from the following metathetical reaction:

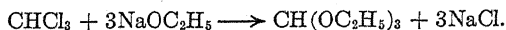


**Derivatives of Ortho Acids.** Compounds of the type  $\text{RC}(\text{OH})_3$  are unknown; all attempts to prepare them lead to the formation of acids. For example, the hydrolysis of a compound containing three halogen atoms on the same carbon atom yields an acid instead of the expected  $\text{RC}(\text{OH})_3$ .



There is some evidence which indicates that such compounds exist in aqueous solutions of acids or in mixtures of an acid and an equimolecular amount of water, but we can not be certain of this. It is convenient to have a name for the unknown class, nevertheless, and they are called *ortho acids*. The corresponding alkyl compounds,  $\text{RC}(\text{OR})_3$ , are known and are called *ortho*

esters. Thus  $\text{HC}(\text{OC}_2\text{H}_5)_3$  is called *ethyl orthoformic ester* (b.p.  $145^\circ$ ). It is prepared by the action of  $\text{CHCl}_3$  on sodium ethylate:



Ortho esters are rapidly hydrolyzed in the presence of acids with the formation of the corresponding acid and alcohol; thus ethyl orthoformic ester yields formic acid and ethyl alcohol. Ortho esters are surprisingly resistant to the action of alkalies.

### STRUCTURE OF ACETIC ACID

At this point some of the reasons for writing the formula of acetic acid as  $\text{CH}_3\text{COOH}$  may be considered. If we can establish its structure, we can write with assurance a similar formula for all other members of the series.

*The analysis and molecular weight of acetic acid show that it must have the molecular formula  $\text{C}_2\text{H}_4\text{O}_2$ .* The reaction with phosphorus trichloride, which yields phosphorous acid and acetyl chloride, proves the presence of an *hydroxyl group* in the molecule (p. 6). We can indicate this development in our knowledge by the provisional formula  $(\text{C}_2\text{H}_3\text{O})(\text{OH})$ . The presence of the *methyl group* attached to a carbon atom in acetic acid is indicated by the following facts:

- (1) Acetic acid is formed by the hydrolysis of  $\text{CH}_3\text{CN}$  (acetonitrile) and by the oxidation of  $\text{CH}_3\text{CH}_2\text{OH}$  both of which contain the grouping  $\text{CH}_3-\text{C}$ .
- (2) On heating sodium acetate ( $\text{C}_2\text{H}_3\text{O}_2\text{Na}$ ) with sodium hydroxide, methane is formed; this is still further evidence of the existence of the  $\text{CH}_3$  group in the molecule.

Taking all these facts into consideration, we can conclude that the acetic acid molecule must contain the grouping  $\text{CH}_3-\text{C}-\text{OH}$ . This leaves one oxygen atom unaccounted for; this can only be connected in one of the following two ways:

$\begin{array}{c} \text{O} \\ \diagup \\ \text{CH}_3\text{C}-\text{OH} \end{array}$ 
or
 $\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{C}-\text{OH} \end{array}$ 
We prefer the second of these alternatives for reasons similar to those given in the case of ethylene (p. 59). Only a few special compounds showing unusual properties contain a trivalent carbon atom; compounds containing a monovalent oxygen atom are rare and peculiar in their reactions. It seems probable, therefore, that in acetic acid neither carbon nor oxygen exhibits unusual valence. We indi-

cate the adjacent unsaturation of the two atoms (C and O) by a double linkage.

The formula  $\text{CH}_3\text{C}(=\text{O})\text{OH}$  may thus be regarded as the consequence of the experimental facts mentioned above. Similar facts and similar reasoning show that in general the fatty acids contain

an alkyl group attached to the group  $-\text{C}(=\text{O})\text{OH}$ .

**The Experimental Basis of Structural Formulas.** It may be well to point out that in general the formulas of the simpler organic compounds are based on many different experimental facts, all of which are consistent with the structure ascribed. In discussing the structure of a substance in an elementary course, it is impossible to cite all the evidence. Therefore, only the most vital facts are given and the reasoning is based on them. As the science of organic chemistry grows, more complicated substances are constantly being investigated. At first, any structural formula rests on only a relatively few experimental facts, and is necessarily tentative; if need be, it is changed when more is known about the substance. Finally, the accumulation of evidence is so great that the formula is generally accepted. Strictly speaking, no structural formula can be said to be proved (with the exception perhaps, of such simple substances as methane and methyl alcohol). The structure of most of the compounds dealt with in this book may be said to have been demonstrated "beyond a reasonable doubt." If, however, tomorrow some investigator should discover an experimental fact clearly inconsistent with an accepted formula, this would reopen the subject for discussion and experimentation.

### QUESTIONS AND ANSWERS

1. Describe briefly the essentials of the industrial methods of preparing: (a) acetic acid; (b) vinegar; (c) formic acid.
2. Define and illustrate the terms: acyl group, carboxyl group, dissociation constant, acid anhydride, acid chloride.
3. Write the structural formulas of: propionyl chloride, butyric anhydride, isobutyryl chloride, potassium propionate, isopropyl butyrate, *n*-octyl isovalerate, 3-ethyl-4-methylpentanoic acid, dimethylethyl-acetic acid.
4. Write equations showing: (a) The laboratory method of preparing

acetic anhydride from acetic acid; (b) the preparation of formic acid from coke; (c) two reactions of formic acid not given by acetic acid.

5. What experimental facts show that  $\text{CH}_3\text{OC}(=\text{O})\text{H}$  is not the formula for acetic acid? What evidence can you cite to rule out the following possibilities  $\text{CH}_2 = \text{C}(\text{OH})_2$ ,  $\text{CH}_2\text{OHCOH}$ ?

6. Write structural formulas for all the isomeric acids of the formula  $\text{C}_4\text{H}_8\text{COOH}$ .

7. Caproic acid,  $\text{C}_6\text{H}_{12}\text{COOH}$ , is only slightly soluble in water and is of approximately the same strength as acetic acid. What would you expect to happen if you treated a concentrated water solution of its sodium salt with: (a) carbon dioxide; (b) hydrochloric acid; (c) ammonia? In which of the following would you expect the pure acid to dissolve: (a) dilute sulfuric acid; (b) ether; (c) dilute sodium acetate solution; (d) dilute sodium carbonate; (e) ammonium hydroxide?

8. Write equations showing how you would prepare: (a) butyric acid from *n*-butyl alcohol; (b) propionic acid from ethyl alcohol; (c) isobutyric acid from propylene; (d) *n*-valeric acid from *n*-butyric acid.

9. How would you decide whether a certain liquid was an acid, an acid chloride, or an acid anhydride?

10. Compare propyl chloride and propionyl chloride, in regard to methods of preparation, physical properties and chemical reactions.

11. Write a balanced equation showing two ways of preparing esters of an organic acid without involving the acid itself.

12. How could you most easily tell whether a certain liquid was an ether or an ester?

13. What is meant by the term "reversible reaction"? What effects have catalysts and increased temperature on a reversible reaction? Illustrate by a brief discussion of the process of esterification.

14. Write structural formulas for all the esters which have the formula  $\text{C}_4\text{H}_8\text{O}_2$ . There are tests which enable one to distinguish methyl from ethyl alcohol. How would these be of service in determining which of the isomers was at hand?

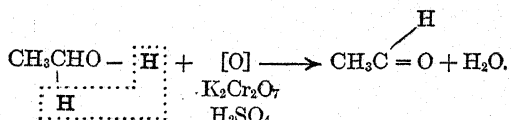
15. Butyl butyrate boils at  $165^\circ$ . Devise a method for preparing it from butyric acid and butyl alcohol which will give as high a yield as possible.

16. Why is thionyl chloride an excellent reagent in many cases for preparing acyl chlorides?

## CHAPTER VI

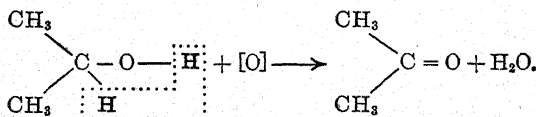
### ALDEHYDES AND KETONES

**Oxidation of Primary Alcohols.** When a primary alcohol is cautiously oxidized, it is possible to isolate a substance intermediate between the alcohol and the corresponding acid. Such a compound is known as an **aldehyde**. For example, if ethyl alcohol is slowly added to a mixture of sodium dichromate and sulfuric acid, and the volatile products allowed to distill, we find in the distillate considerable quantities of **acetaldehyde**,  $\text{CH}_3\text{CHO}$ :



On the other hand, if we arrange the apparatus with a reflux condenser so that the volatile aldehyde is returned to the oxidizing agent, the product is acetic acid, because the aldehyde is further oxidized to the acid.

**Oxidation of Secondary Alcohols.** When a secondary alcohol is oxidized, a ketone is formed:

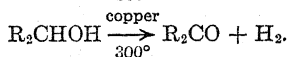
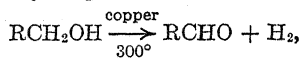


Here there is little danger that the oxidation will proceed too far; ketones are oxidized only with difficulty and never to a product with the same number of carbon atoms.

It will be noted that both these processes of oxidation consist in the removal of two hydrogen atoms which have been indicated by heavy print in the formulas. The process is really one of **dehydrogenation**; this term is often applied to it. We may suppose that the function of the oxidizing agent is to supply oxygen to combine with the two hydrogen atoms and form water.

In the presence of metallic copper at  $300^\circ$ , primary and second-

ary alcohols spontaneously lose hydrogen and form aldehydes or ketones and gaseous hydrogen.



This provides a convenient method of preparing ketones and aldehydes from the corresponding alcohols. A laboratory apparatus for such a catalytic dehydrogenation is shown in Fig. 16.

Copper chromite (p. 100) is also used as a catalyst to dehydrogenate primary and secondary alcohols. In many cases the yields are better when this catalyst is employed.

**Behavior of Tertiary Alcohols with Oxidizing Agents.** An examination of the structure of a tertiary alcohol would lead one to predict that an oxidation process similar to that of primary and secondary alcohols would be impossible in this case. There is no hydrogen atom attached to the C—OH group. Tertiary alcohols are, indeed, oxidized with difficulty, and are broken into smaller molecules by the reaction.

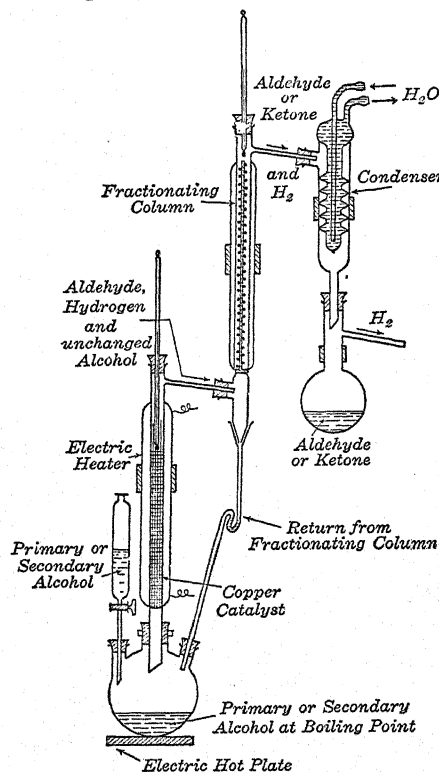


Fig. 16. Apparatus for the preparation of aldehydes or ketones by the catalytic dehydrogenation of primary or secondary alcohols at 200°–300°.

We may thus say that *only primary and secondary alcohols can be oxidized to compounds containing the same number of carbon atoms as the original alcohol*. Since aldehydes, but not ketones, can be further oxidized, it is evident also that *only primary alcohols may be oxidized to an acid with the same number of carbon atoms*.

**Distinction between Primary, Secondary and Tertiary Alcohols.**

This difference in the behavior of primary, secondary, and tertiary alcohols on oxidation enables us to distinguish between them. The student should convince himself that this is a necessary consequence of the structural theory by writing the formulas of the isomeric alcohols and the equations for the reactions.

**ALDEHYDES AND KETONES**

**The Carbonyl Group.** Aldehydes and ketones both contain the group  $\text{>C} = \text{O}$ ; this is known as the *carbonyl* group. Since they both contain this reactive group, they have many chemical properties in common. The differences between aldehydes and ketones are due to the fact that in the case of the aldehydes,

$\text{H} \diagdown$   
 $\text{R} - \text{C} = \text{O}$ , we have one alkyl group and one hydrogen atom attached to the carbonyl group, and in ketones,  $\begin{matrix} \text{R} \\ \text{R} \end{matrix} \text{>C} = \text{O}$ , two alkyl groups.

$\text{H} \diagup$   
 It is customary to write the formula of an aldehyde,  $\text{RC} = \text{O}$ , as  $\text{RCHO}$ . Formulas corresponding to  $\text{RCOH}$  are never used as this might signify that the hydrogen was attached to oxygen.

**Physical Properties of Aldehydes.** The physical properties of the lower members of the homologous series of aldehydes are given below. The first five all have a peculiar sharp odor.

**PHYSICAL PROPERTIES OF THE SIMPLER ALDEHYDES**

NAME	FORMULA	BOILING POINT	SOLUBILITY GRAMS PER 100 GRAMS OF WATER
Formaldehyde	$\text{HCHO}$	$- 21^\circ$	miscible
Acetaldehyde	$\text{CH}_3\text{CHO}$	$+ 20^\circ$	miscible
Propionaldehyde	$\text{CH}_3\text{CH}_2\text{CHO}$	$+ 49^\circ$	20
<i>n</i> -Butyraldehyde	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$	$+ 76^\circ$	3.6
Isobutyraldehyde	$(\text{CH}_3)_2\text{CHCHO}$	$+ 61^\circ$	11
<i>n</i> -Valeraldehyde	$\text{CH}_3(\text{CH}_2)_3\text{CHO}$	$+ 102^\circ$	
<i>n</i> -Capronaldehyde	$\text{CH}_3(\text{CH}_2)_4\text{CHO}$	$+ 128^\circ$	
<i>n</i> -Heptaldehyde	$\text{CH}_3(\text{CH}_2)_5\text{CHO}$	$+ 155^\circ$	

The higher aldehydes have a pleasant odor. Some of them occur in fruits and plants; for example, nonyl aldehyde  $\text{C}_9\text{H}_{17}\text{CHO}$  is found in geranium oil.



A similar but much better process has been devised for accomplishing the same purpose. The vapor of the acid in question is passed through a hot tube containing the oxide of manganese,  $\text{MnO}$ , as a catalyst (Fig. 17). On the surface of the catalyst a reaction takes place, yielding the

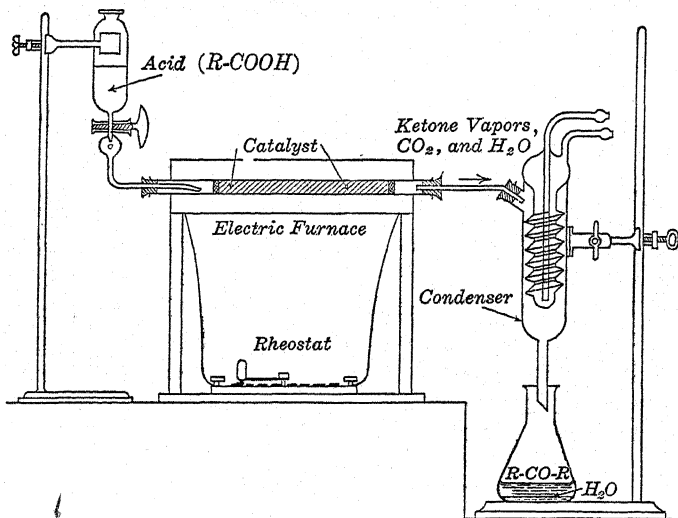
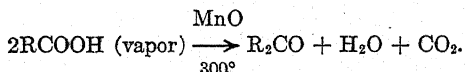


Fig. 17. Apparatus for the preparation of ketones from acids by means of a catalyst of  $200^{\circ}$ – $300^{\circ}$ .

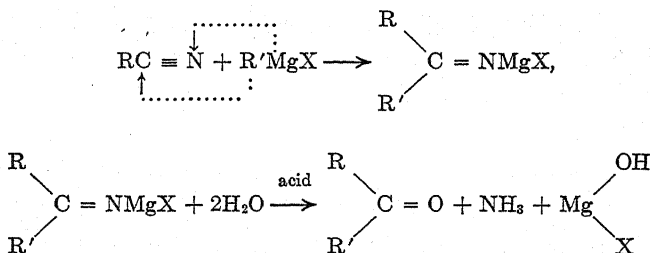
ketone. The yields are far superior to those obtained by the method involving the use of the calcium salts of the acids.



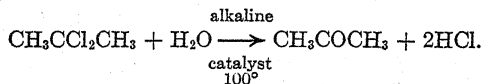
Mixed ketones, for example, methyl ethyl ketone, may be prepared by passing a mixture of the two acids in question over the catalyst mentioned above. In addition to the mixed ketone, a mixture of the other two possible ketones is always formed. For this reason it is preferable to prepare such mixed ketones by oxidizing the corresponding secondary alcohol, if it can be readily procured.

- (b) **From Nitriles.** The action of a Grignard reagent on a nitrile yields a magnesium compound which is easily hydrolyzed on treatment with acid forming a ketone and am-

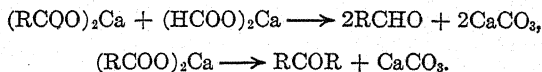
monia. The general equations are given below, the symbol  $R'$  being used to indicate that the resulting ketone may be either symmetrical or unsymmetrical:



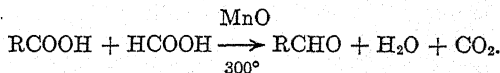
- (c) **From Dihalides.** The hydrolysis of a compound having two halogen atoms on the same carbon atom might be expected to produce a substance having the group  $\text{C}(\text{OH})_2$ . Actually either an aldehyde or ketone is formed. Except in a few cases (see chloral, p. 125) compounds containing two hydroxyl groups on the same carbon atom are unstable, and lose water forming a carbonyl group:



**Preparation of Aldehydes.** Similar procedures may be used for the production of aldehydes. The destructive distillation of a mixture of the calcium salt of an acid and calcium formate yields some aldehyde together with the corresponding ketone:

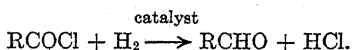


Similarly, by passing the vapors of an acid and formic acid over a suitable catalyst, considerable aldehyde is formed:



The problem of reducing acids directly to an aldehyde has not been solved. Acid chlorides, however, may be reduced catalytically by passing hydrogen through a solution of the acid chloride in dry benzene or xylene (p. 325) in which is suspended a catalyst

of palladium on barium sulfate. The reaction is generally carried out at the boiling point of the solvent.



**Oxidation of Aldehydes.** The chief difference between aldehydes and ketones is that the former are very easily oxidized to an acid while the latter are oxidized only with difficulty. Furthermore, when ketones are oxidized, the carbon linkage is broken, and acids with fewer carbon atoms are the products. The difference in the ease of oxidation is the basis for several tests which enable us to distinguish between the two classes of substances. When aldehydes are warmed with an **ammoniacal solution of silver nitrate**, they precipitate metallic silver which often comes down in the form of a beautiful mirror. The aldehyde is oxidized to the corresponding acid (in this alkaline solution as the corresponding salt):



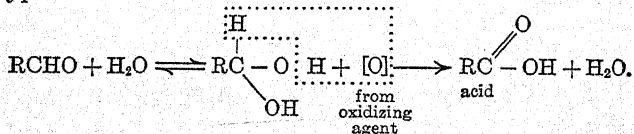
Similarly, when an alkaline solution of copper hydroxide containing sodium tartrate (essentially copper hydroxide in solution) — **Fehling's solution** — is warmed with an aldehyde, red cuprous oxide is precipitated:



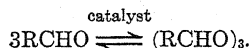
These tests are very easy to carry out and are frequently employed. Ammoniacal silver nitrate and Fehling's solution are often spoken of as *mild* oxidizing agents, since many substances, such as alcohols, are not attacked by these reagents.

**Mechanism of the Oxidation.** The oxidation of aldehydes is probably in reality another case of dehydrogenation. There is considerable evidence to indicate that the aldehydes are hydrated in water solution; these hydrates, like the primary and secondary

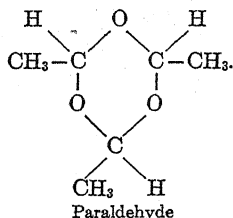
alcohols, have the group  $\text{C} \begin{array}{c} \text{H} \\ \diagup \\ \text{C} - \text{OH} \end{array}$ . The following equation represents the course of the oxidation of aldehydes according to this hypothesis:



**Polymerization of Aldehydes.** Aldehydes and ketones differ in still another respect. When an aldehyde is treated with a small amount of mineral acid, it is almost completely *polymerized* (p. 76). The polymer is a substance which has a molecular weight three times that of the aldehyde:



The reaction is reversible in the presence of acid. The polymer in the case of acetaldehyde is known as **paraldehyde**. It is a much higher-boiling liquid than acetaldehyde and, unlike acetaldehyde, is insoluble in water. It has none of the characteristic reactions of the aldehydes; for example, it will not reduce Fehling's solution. In the polymer the three aldehyde molecules are joined together in a ring containing alternate carbon and oxygen atoms. Paraldehyde is used in medicine as a hypnotic.



At low temperatures acetaldehyde is polymerized by dilute sulfuric acid to a crystalline solid known as **metaldehyde**. Like paraldehyde it shows no aldehydic properties. It can be converted into acetaldehyde by distilling with dilute acid. It burns in air with a non-luminous flame and is marketed as a solid fuel for household use in place of "solid alcohol." The trade name for it is "meta." Metaldehyde differs from paraldehyde in that it is a tetramer,  $(\text{CH}_3\text{CHO})_4$ .

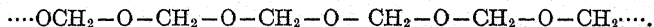
**Another Example of a Reversible Reaction.** A consideration of the reversible polymerization of an aldehyde is of interest. The equilibrium with most aldehydes is very much in favor of the polymer. That is, when pure acetaldehyde is treated with a few drops of sulfuric acid, it rapidly polymerizes until more than 95 per cent of the material is present as paraldehyde; the process then reaches equilibrium. In the same way, when pure paraldehyde is treated with a little acid, a few per cent of it depolymerizes, but no more. We are here dealing with a state of dynamic equilibrium, just as in the case of esterification and hydrolysis.

**Importance of the Catalyst.** It must be clearly borne in mind that the reaction is reversible *only* in the presence of a suitable catalyst, such as a mineral acid. Pure acetaldehyde or pure paraldehyde may be kept unchanged for a long period of time and may be distilled without decomposition. The

rate of the reaction in either direction only becomes appreciable in the presence of a catalyst. When the rate is relatively rapid, owing to the presence of a catalyst, we may say that we are dealing with a *mobile equilibrium*. Under these conditions it is easy to convert the one substance into the other. For example, to prepare paraldehyde we treat cold acetaldehyde with a few drops of acid, and after a few minutes, when equilibrium has been established, wash away with water or dilute alkali both the unchanged aldehyde and the catalyst. The paraldehyde can then be dried, distilled, and kept just like any other organic substance.

To convert paraldehyde (b.p.  $124^{\circ}$ ) into acetaldehyde it is only necessary to add a few drops of mineral acid and slowly distill. Since the acetaldehyde boils at  $20^{\circ}$ , it rapidly volatilizes and is thus removed from the equilibrium mixture. More paraldehyde then depolymerizes, and this process continues until all the paraldehyde has depolymerized and distilled over in the form of acetaldehyde. This is an excellent example of the completion of a reversible reaction by removing one of the products.

**Polymers of Formaldehyde.** Trioxymethylene,  $(\text{HCHO})_3$ , is a crystalline solid which has no aldehyde properties. On heating, it decomposes to form gaseous formaldehyde. Its cyclic structure is analogous to that of paraldehyde. In addition to this polymer, formaldehyde forms solid polymers of unknown molecular weight,  $(\text{HCHO})_x$ . These are known as **paraformaldehydes** or **polyoxymethylenes**. They are amorphous solids insoluble in all solvents; they show no aldehydic reactions, and on heating decompose to give formaldehyde. They are formed by evaporating an aqueous solution of the aldehyde and on treating an alcoholic solution with acid. It has been shown recently that the large molecule which is present in these polymers is composed of a chain of 40 to 100 formaldehyde units. A portion of this chain may be represented thus:

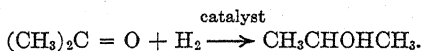
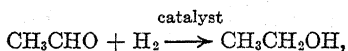


Depending on the method of formation the terminal groups of the long chain are either  $-\text{OH}$  or  $-\text{OCH}_3$  (the latter from the methyl alcohol used in the preparation). Acetaldehyde and the higher homologs of formaldehyde do not form such long-chain polymers under usual conditions. However, by subjecting the liquid aldehyde to very high pressure (5,000 to 10,000 atmospheres) for some hours, such high-molecular polymers are formed in the case of the higher aldehydes. They resemble paraformaldehyde in their physical properties, but slowly revert to the liquid aldehyde when kept at atmospheric pressure.

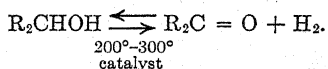
## ADDITION REACTIONS OF THE CARBONYL GROUP

So far, we have stressed the differences between aldehydes and ketones. We shall now consider their many similarities. The carbonyl group,  $>\text{C}=\text{O}$ , in both substances is very reactive and adds many reagents. Such addition reactions, as we have seen, are characteristic of substances with a double linkage (p. 63). The double linkage in aldehydes and ketones is between carbon and oxygen in contrast with that in ethylene which involves only carbon atoms. The reagents which add to the carbonyl group and to the ethylene linkage are, therefore, for the most part very different.

**Hydrogenation.** Aldehydes and ketones are both readily hydrogenated to the corresponding primary and secondary alcohols by the use of hydrogen and a catalyst:



This is the reversal of the process by which aldehydes and ketones may be prepared, and at temperatures of about  $200^\circ$  in the presence of copper or nickel, there is a mobile equilibrium; with increasing temperature the reaction proceeds to the right:

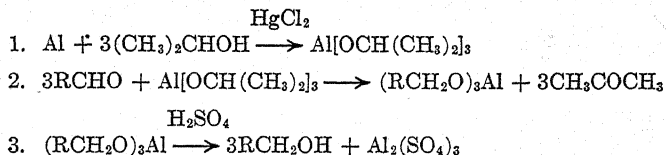


At room temperature, hydrogen and a suitable catalyst will completely hydrogenate aldehydes and ketones; above  $200^\circ$  the reverse reaction is evident. The aldehydes, ketones, and alcohols undergo other reversible reactions at still higher temperatures so that the dehydrogenation process (unlike the hydrogenation) is never quantitative.

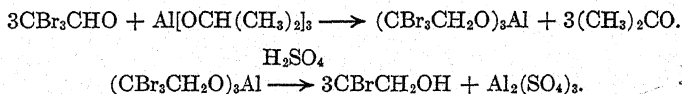
**Reduction.** Hydrogen may also be added to the carbonyl group by using some reagent which liberates "nascent hydrogen." For example, zinc and acid, sodium and alcohol, or sodium amalgam and water are often employed. We shall use the symbol  $[\text{H}]$  for the hydrogen which comes from such reducing agents. These reagents usually reduce aldehydes and ketones to alcohols:



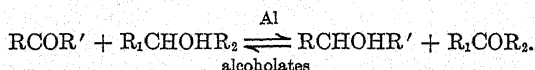
An effective reagent for the reduction of the carbonyl group of aldehydes and ketones is aluminum isopropylate. This is made by allowing aluminum shavings to react with isopropyl alcohol in the presence of mercuric chloride as a catalyst. The steps of the reactions are:



The advantage of this reducing agent lies in the fact that it is, in a sense, specifically a reagent for aldehydes and ketones. It does not affect the carbon-carbon double linkage nor cause the replacement of a halogen atom by hydrogen. In most instances, hydrogen gas and a catalyst as well as the usual sources of "nascent hydrogen" are more general in their action. For example, the reduction of tribromo or trichloroacetaldehyde with most reagents results in the formation of either acetaldehyde or ethyl alcohol. With aluminum isopropylate, however, only the carbonyl group is reduced. The tribromoethyl alcohol,  $\text{CBr}_3\text{CH}_2\text{OH}$ , which can be thus produced is used as an anesthetic under the name of *avertin*. The reaction may be written:

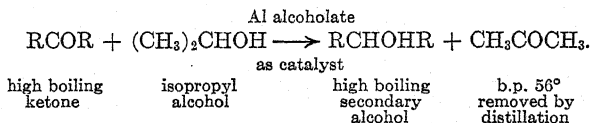


It has been found that the aluminium salt of the isopropyl alcohol is essentially a catalyst for the transfer of hydrogen from the secondary alcohol to the ketone or aldehyde. Indeed, the aluminium salt of tert. butyl alcohol may be employed as the catalyst and other secondary alcohols beside isopropyl alcohol will then enter into a reaction with aldehydes or ketones. In solution at temperatures of 40°–100°, the reaction slowly reaches an equilibrium. The composition of the equilibrium mixture depends on the nature of the carbonyl compound and the alcohol, the temperature and, of course, the concentration of factors and products. We may write the general equation for the reversible balanced reaction as,

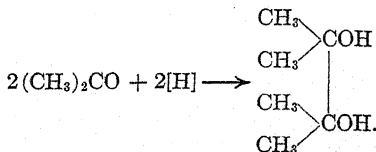


There is an obvious analogy between this reversible reaction and the one written in the preceding section for the gaseous phase in the presence of a

catalyst. In the presence of an aluminum alcoholate catalyst in solution, the two carbonyl compounds  $\text{RCOR}'$  and  $\text{R}_1\text{COR}_2$  are competing for two hydrogen atoms. The energy relations are such that an aldehyde has greater affinity for hydrogen than a ketone. Therefore, the reaction will proceed far to the right if an aldehyde ( $\text{R}' = \text{H}$ ) reacts with a secondary alcohol, but will be essentially balanced if two ketones are involved (all  $\text{R}'$ 's = alkyl). Even under this circumstance, however, a ketone may be reduced nearly quantitatively by isopropyl alcohol if the boiling point of the desired product is much higher than acetone. A slow distillation removes the acetone and thus upsets the balanced equilibrium causing the reaction to proceed completely to the right.

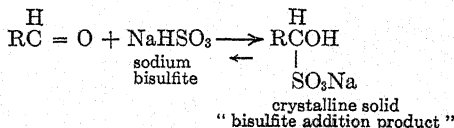


**Dimolecular Reduction.** Ketones can be also reduced to dihydroxy compounds known as **pinacones** or **pinacols**; this type of reduction involves the joining of two molecules and is called *dimolecular reduction*. It is accomplished by using metals in alkaline solution, in particular, amalgamated magnesium.



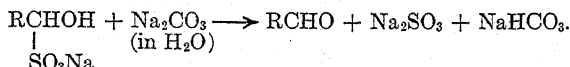
The simplest of these which is prepared from acetone is called **pinacol**  $(\text{CH}_3)_2\text{COHCOH}(\text{CH}_3)_2$ . It is a liquid boiling at  $172^\circ$ , and forms a white crystalline hydrate when treated with water.

**Bisulfite Reaction.** Ketones which contain one methyl group adjacent to the carbonyl group, and *all* aldehydes, combine with sodium bisulfite to form solid crystalline compounds soluble in water but insoluble in an excess of sodium bisulfite solution:



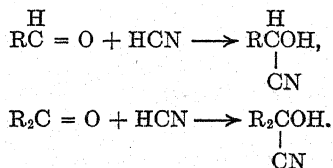
It is still unsettled whether in the bisulfite addition compound the sulfite group is linked to carbon through oxygen or sulfur.

**Purification of Aldehydes and Methyl Ketones.** On shaking an aldehyde with sodium bisulfite solution and cooling, a crystalline mass of the bisulfite addition product is formed which can be filtered off. This reaction is taken advantage of in purifying aldehydes and methyl ketones. The reaction is reversible, but the equilibrium is such that most of the material is present as the addition product; by using sufficient excess of bisulfite practically all of the aldehyde can be converted into the desired product. It can be further purified by recrystallization. To obtain the aldehyde again, the addition product is warmed in water solution with sodium carbonate; this reacts with the bisulfite which is in equilibrium, neutralizing it, and forming sodium sulfite. The reaction thus goes to completion:



The aldehyde is obtained from the water solution by distilling or extracting with an organic solvent. Exactly the same procedure can be used for purifying ketones which contain a methyl group. Other ketones do not form bisulfite addition products.

**Addition of Hydrocyanic Acid.** Hydrocyanic acid combines with aldehydes and ketones; the hydrogen atom attaches itself to the oxygen atom and the CN group to the carbon atom. The product is a hydroxynitrile which is often called a **cyanhydrin**:



Because hydrocyanic acid is so dangerous to handle, the cyanhydrins are often prepared by treating the bisulfite addition product with a solution of potassium cyanide. A small amount of hydrocyanic acid is formed by the action of free sodium bisulfite on the potassium cyanide. This hydrocyanic acid then combines with the aldehyde which is in equilibrium with the bisulfite addition product. The equilibrium conditions are thereby upset and more bisulfite addition product dissociates to produce more free aldehyde and more free bisulfite; the latter further liberates free hydrocyanic acid which again combines with an equivalent amount of free aldehyde. In this way the reaction proceeds to completion without any large quantity of aldehyde or hydrocyanic acid ever being present in the reaction mixture.

**Aldol Condensation.** The addition reactions of the carbonyl group include a peculiar type of reaction in which one molecule of an aldehyde adds to the carbonyl group of another molecule.



boiler continuously by passing through the porous vessel which holds the catalyst. In its passage through the solid catalyst the liquid acetone is converted to diacetone alcohol as far as the equilibrium conditions permit (a few per cent). The diacetone alcohol being much less volatile than the acetone does not volatilize and accumulates in the boiler; since no catalyst is present, the concentration of product may greatly exceed the equilibrium conditions. In fact, in this way nearly all of the acetone may be converted into diacetone alcohol. It is interesting that this product though perfectly stable when pure, immediately decomposes when treated with alkali forming the equilibrium mixture which is largely acetone. The apparatus used in this preparation (Fig. 18) is known as a *Soxhlet extractor* and is employed whenever a liquid is to be passed continuously through a solid as in the extraction of solid fatty material by ether.

**Reaction with the Grignard Reagent.** Both aldehydes and ketones combine with the Grignard reagent. The first product of the reaction is a magnesium compound which is easily hydrolyzed by water or decomposed by acids, yielding an alcohol. In this manner *aldehydes yield primary or secondary alcohols and ketones tertiary alcohols*. The reactions are illustrated by the following equations using acetaldehyde and methyl magnesium iodide, and acetone and methyl magnesium iodide as the examples:

(1) *Synthesis of a Primary Alcohol.* If formaldehyde (as a gas or sometimes as the solid polymer) is added to a Grignard reagent, the decomposition of the product yields a primary alcohol:

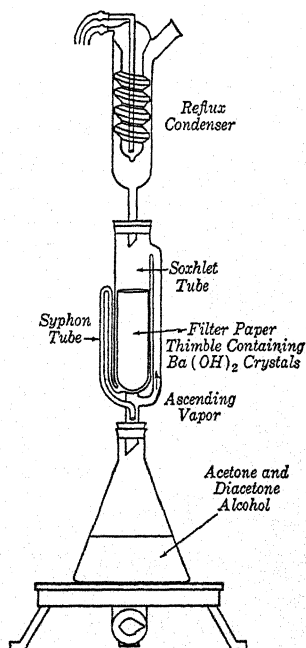
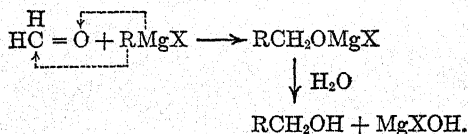
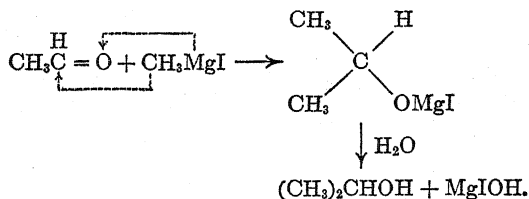
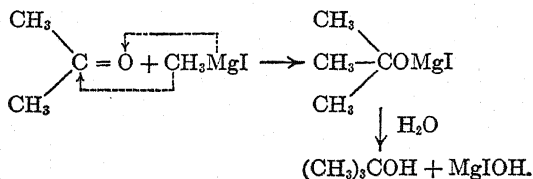


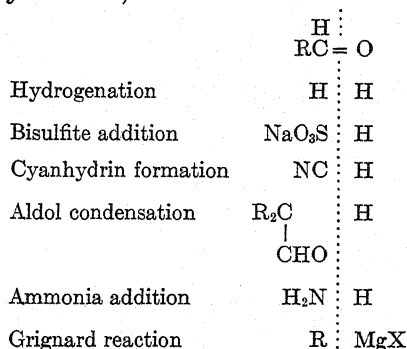
Fig. 18. Soxhlet extraction apparatus used in the conversion of acetone to diacetone alcohol.

(2) *Synthesis of a Secondary Alcohol:*(3) *Synthesis of a Tertiary Alcohol:*

Since a variety of primary, secondary, and tertiary alcohols can thus be prepared, these three reactions are of the greatest importance. It will be noted that in these reactions the magnesium atom together with the halogen atom attaches itself to the oxygen, and the alkyl group goes to the carbon atom. These reactions proceed rapidly at room temperature in ether solution. They are usually carried out by preparing the Grignard reagent in ether solution as described in Chap. II, and then slowly adding the aldehyde or ketone. The reaction mixture is then treated with the ice cold ammonium chloride solution or acid, which hydrolyzes the addition product and keeps the basic magnesium salt ( $\text{MgXOH}$ ) in solution. Lithium alkyls (p. 28) may be used in place of the Grignard reagent in the above reactions.

**A Summary of the Addition Reactions.** In all the addition reactions of the carbonyl group, except the hydrogenation, we have been dealing with the addition of unsymmetrical reagents. It is important to remember the way in which such reagents add. A very simple rule holds in the case of carbonyl compounds; *a hydrogen atom or a metal adds to the oxygen*, the residue adds to the carbon. All the reagents (except  $\text{RMgX}$ ) are substances with an active hydrogen atom. The following diagram illus-

trates the addition reactions of aldehydes (all of these also take place with methyl ketones):

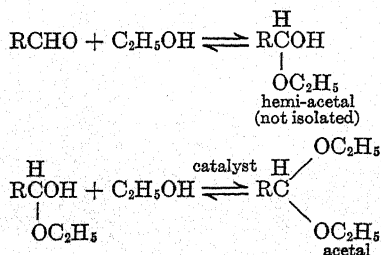


The *addition of ammonia* has been included in this diagram because there is evidence that aldehydes do combine with ammonia to give products of the type  $\text{RCHOHNH}_2$  (called an aldehyde ammonia); but in most cases this reaction is followed by other reactions yielding complex products.

**Reaction of Aldehydes with Alcohols.** Alcohol and water might be added to the diagram given above since the addition com-

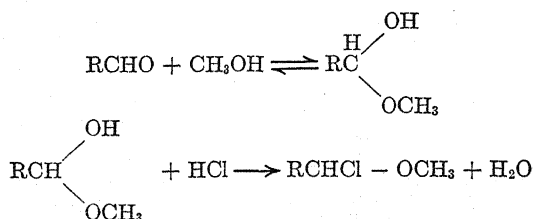
pounds of the type  $\text{RCH}(\text{OH})_2$  and  $\text{RCH} \begin{array}{c} \text{OH} \\ \diagup \\ \text{OC}_2\text{H}_5 \end{array}$  are probably formed

in aqueous and alcoholic solutions of aldehydes. However, except in the case of a few chloroaldehydes (p. 125) the products are too unstable to isolate. If an aldehyde is treated with an alcohol in the presence of calcium chloride or a trace of acid, a reaction takes place which probably proceeds through the primary addition product of the aldehyde and alcohol. The final product is known as an **acetal**, the intermediate as a **hemi-acetal**:



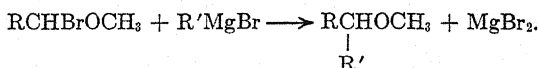
The acetals are hydrolyzed by boiling with aqueous acids; they are insensitive to bases.

When a mixture of aldehydes and alcohols is treated with an excess of hydrogen chloride or hydrogen bromide gas the product is an alpha halogen ether. The course of the reaction is probably as follows:

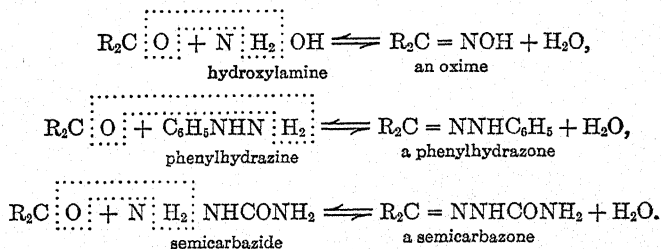


Thus  $\alpha$ -chloromethyl ether,  $\text{CH}_2\text{Cl}-\text{O}-\text{CH}_3$ , is made from formaldehyde, methyl alcohol, and hydrogen chloride.

Alpha halogenated ethers react readily with the Grignard reagent because of their highly reactive halogen. This reaction is utilized to prepare many higher ethers:

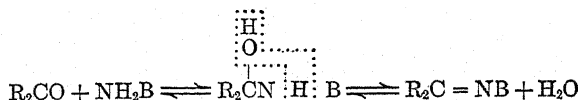


**Condensation with Ammonia Derivatives.** It has been found that aldehydes and ketones react with derivatives of ammonia to form unsaturated compounds which in many instances are crystalline solids. If hydroxylamine,  $\text{NH}_2\text{OH}$ , is used, the compounds are called **oximes**, and if phenylhydrazine,  $\text{C}_6\text{H}_5\text{NHNH}_2$ , is used, the compounds are known as **phenylhydrazones**. With semicarbazide,  $\text{NH}_2\text{NHCONH}_2$ , **semicarbazones** are formed.



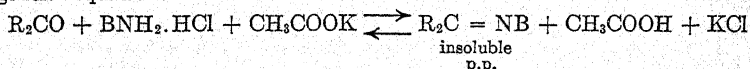
Similar reactions occur with aldehydes and the products are known by the same general names. It is convenient to remember that these three reagents which condense with aldehydes and ke-

tones have the general formula  $\text{BNH}_2$ , and that the products have the general formula  $\text{R}_2\text{C} = \text{NB}$  in the case of ketones, and  $\text{RCH} = \text{NB}$  in the case of aldehydes (B is OH for the oximes,  $\text{C}_6\text{H}_5\text{NH}$  for the phenylhydrazones, and  $\text{NHCONH}_2$  for the semicarbazones). It is often supposed that the condensation proceeds through the intermediate formation of an addition product  $\text{R}_2\text{COHNHB}$  which then loses water; if this is the case these reactions may be thought of as a special case of the ammonia addition reaction mentioned above:

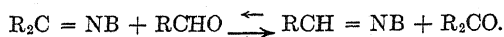


**Identification of Aldehydes and Ketones.** The identification of very small amounts of liquids is always a very difficult matter in the laboratory. The identification of small amounts of solids is relatively easy if the solids have a melting point between room temperature and  $200^\circ$ . The simple aldehydes and ketones are all liquids, and the problem of identifying them therefore resolves itself into the problem of converting them into crystalline solids with sharp melting points. This is mostly done by means of one of the three condensation reactions just described. In fact hydroxylamine, phenylhydrazine, and semicarbazide are often called "carbonyl group reagents" because they form crystalline condensation products with most aldehydes and ketones. For the simplest aldehydes and ketones, the last two reagents are used since the oximes of low molecular weight are liquid. The phenylhydrazones and semicarbazones formed from practically all aldehydes and ketones are crystalline solids with a sharp melting point.

The reaction is usually carried out in aqueous solution or a mixture of alcohol and water if the carbonyl compound is insoluble in water. The reagent is usually added in the form of its hydrochloride. (Like ammonia, these reagents are bases and form salts with acids.) Since the reaction will not proceed if any mineral acid is present in the solution, potassium acetate is added in excess to react with the hydrochloric acid. The product separates as a crystalline solid, a fact which causes the balanced reaction to go more nearly to completion. The entire reaction is thus represented by the following general equation:



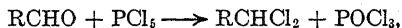
The composition of the equilibrium mixture and the speed at which equilibrium is attained depends on the aldehyde or ketone, the reagent, and the acidity of the solution. Under comparable conditions the condensation with ketones is less complete (at equilibrium) than with aldehydes. For this reason aldehydes may be used to regenerate ketones from their condensation products; acetic acid is used to accelerate the reaction:



**Tests for Aldehydes.** The fuch sine test and the reaction with ammoniacal silver nitrate are often used for distinguishing aldehydes from ketones. The fuch sine test consists of adding a solution of the material to a solution of fuch sine (magenta) which has been barely decolorized with sulfur dioxide; such a solution is known as **Schiff's reagent**. If an aldehyde is present, a bright pink color soon appears. Ketones do not give this test and do not reduce ammoniacal silver nitrate (p. 111).

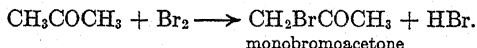
#### REACTIONS INVOLVING HALOGEN

**Replacement of Carbonyl Oxygen.** The carbonyl oxygen in aldehydes and ketones may be replaced by the action of phosphorus pentachloride:



The dichloro compounds thus produced undergo hydrolysis on boiling with alkali and regenerate the carbonyl compound.

**Replacement of Hydrogen by Halogen.** By the action of chlorine or bromine on a ketone, one or more hydrogen atoms adjacent to the carbonyl group are readily replaced by halogen:



It is very interesting that the hydrogen atom replaced is the same one that is active in the aldol condensation. We thus see that as a general rule the hydrogen atoms on the *carbon adjacent to the carbonyl group* are active. This carbon atom is often called the *alpha* carbon atom since by one method of nomenclature the position of the substituent in aldehydes or ketones is denoted by

$\gamma \quad \beta \quad \alpha$

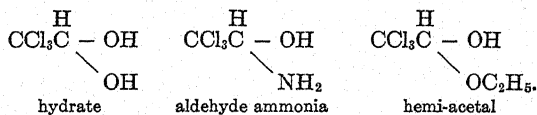
Greek letters, thus;  $CH_3CH_2CHBrCHO$ , is known as **alpha bromobutyraldehyde**.

The direct interaction of aldehydes and halogen leads to a mixture of products. The cyclic trimers (p. 112), however, can often be brominated with the replacement of only one hydrogen per carbonyl group. The alpha halogen ketones and aldehydes are reactive substances and are used in syntheses. They are extremely lachrymatory in their action and the bromoacetones are used as a "tear gas."

**Chloral.** Trichloroacetaldehyde, commonly called *chloral*, can be prepared by treating acetaldehyde with chlorine water or by the action of chlorine on ethyl alcohol. In the latter case, the chlorine first oxidizes the alcohol to acetaldehyde and then chlorinates this substance. Chloral is an oily liquid which boils at 97° and has the peculiar property of combining with a molecule of water, forming the crystalline solid, **chloral hydrate**,  $\text{CCl}_3\text{CH}(\text{OH})_2$ . This finds a limited use in medicine as an hypnotic.

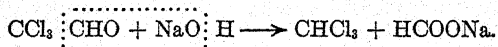
Chloral hydrate is of scientific interest because it appears to be one of the few stable compounds in which two hydroxyl groups are attached to the same carbon atom. It easily loses water on heating, forming the aldehyde. Some prefer to write the formula  $\text{CCl}_3\text{CHO} \cdot \text{H}_2\text{O}$  instead of  $\text{CCl}_3\text{CH}(\text{OH})_2$ , leaving it undecided as to whether a dihydroxy compound is really at hand. The fact that chloral hydrate does not affect Schiff's reagent whereas chloral does, is evidence in favor of the dihydroxy formula. Apparently the reaction between chloral and Schiff's reagent is faster than the hydration.

Chloral also combines with one molecule of alcohol to form a compound which is probably one of the few examples of a hemiacetal (p. 121):

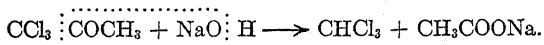


With one molecule of ammonia chloral gives a true aldehyde ammonia.

**The Haloform Reaction.** Chloral is rapidly decomposed on treatment with aqueous sodium hydroxide yielding chloroform,  $\text{CHCl}_3$ , and sodium formate:

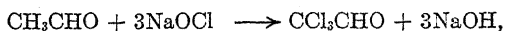
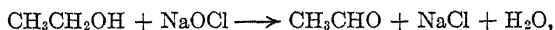


A similar reaction takes place with trichloroacetone,  $\text{CCl}_3\text{COCH}_3$ ; here sodium acetate is one of the products:

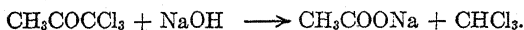
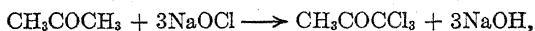


This reaction is taken advantage of in preparing chloroform (p. 133). Sodium hypochlorite acts on *acetaldehyde or any methyl ketone* to form chloroform. It also acts on substances which are readily *oxidized to acetaldehyde or a methyl ketone*, since it is both an oxidizing agent and a chlorinating agent. The reactions proceed very rapidly and no intermediates can be isolated under these conditions:

Chloroform from alcohol,



Chloroform from acetone,



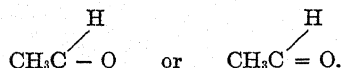
A similar reaction is given if sodium hypobromite ( $\text{NaOBr}$ ) or sodium hypoiodite ( $\text{NaOI}$ ) is used in place of the hypochlorite; the halogen-containing products are **bromoform**,  $\text{CHBr}_3$ , or **iodoform**,  $\text{CHI}_3$ . The latter is a yellow solid with a characteristic odor, and is easily identified.

The action of one of these reagents on a methyl ketone is a convenient way of preparing an acid  $\text{RCOOH}$  from the *methyl ketone*,  $\text{RCOCH}_3$ .

**The Iodoform Test for Ethyl Alcohol.** Generally in the laboratory, sodium hypoiodite is prepared by treating an aqueous solution of iodine in an iodide with sodium hydroxide. Such a solution gives an immediate precipitate of iodoform with acetone, and when warmed with ethyl alcohol gives a similar precipitate. Since methyl alcohol does not form iodoform when treated with sodium hypoiodite, this test is often used to *distinguish ethyl from methyl alcohol*. Acetone, acetaldehyde, isopropyl alcohol and a number of other substances also will give the test.

**Structure of Acetaldehyde.** The decomposition of chloral by sodium hydroxide to give chloroform and sodium formate is an important piece of evidence in regard to the structure of chloral and in turn of acetaldehyde itself. Chloroform must contain three chlorine atoms attached to the carbon atom (no other arrangement is possible), and, since it is easily formed from chloral, the group  $\text{CCl}_3$  must also be present in this substance. Chloral, in turn, is formed by the replacement of three hydrogen atoms in acetaldehyde by three chlorine atoms; hence the group  $\text{CH}_3$  must be present in acetaldehyde. We can thus write acetaldehyde,  $\text{C}_2\text{H}_4\text{O}$ , as  $\text{CH}_3(\text{CHO})$ , without for the time being committing ourselves as to the nature of the group in parenthesis.

The preparation of acetaldehyde from ethyl alcohol and its easy reduction to this same substance is clear indication that the two carbon atoms are linked to each other and not through oxygen. The oxidation to acetic acid is also evidence of the same fact. The aldehyde contains no hydroxyl group since it does *not* form  $\text{H}_3\text{PO}_3$  with  $\text{PCl}_3$ ; therefore, the hydrogen and oxygen must be attached as follows:



Our reasons for preferring the second formula with a double linkage are exactly those given in connection with the structure of acetic acid (p. 102).

**The Structure of Ethylene.** It will be remembered that the formula  $\text{CH}_3\text{CH} \angle$  or  $\text{CH}_3\text{CH}$  for ethylene was discarded (p. 59) because ethylene dichloride is  $\text{CH}_2\text{ClCH}_2\text{Cl}$ . We shall now consider the facts which show that the addition product of ethylene and chlorine is the  $\alpha, \beta$  dichloro compound. We have just seen

$\begin{array}{c} \text{H} \\ \diagup \\ \text{CH}_3\text{C} \end{array}$

that acetaldehyde must have the structure  $\text{CH}_3\text{C} = \text{O}$ ; the dichloride formed by replacing the oxygen by two chlorine atoms must, therefore, be  $\text{CH}_3\text{CHCl}_2$ . This is an entirely different substance from the chloride made by adding chlorine to ethylene. Only two isomers are possible, therefore, since that prepared from acetaldehyde must be  $\text{CH}_3\text{CHCl}_2$ ; the one from ethylene is  $\text{CH}_2\text{ClCH}_2\text{Cl}$ . If the chlorine addition product from ethylene had been identical with that formed from acetaldehyde and

$\text{PCl}_5$ , then the formula  $\text{CH}_2\text{CH}$  for ethylene would have been established. No such hydrocarbon has ever been prepared in spite of numerous attempts. Apparently, hydrocarbons with divalent carbon atoms are not stable.

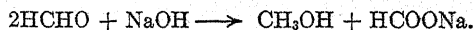
#### A FEW INDUSTRIALLY IMPORTANT ALDEHYDES AND KETONES

A number of aldehydes and ketones are commercially available. Of these the most important are **formaldehyde**, **acetaldehyde**, and **acetone**. They were long prepared from methyl alcohol, ethyl alcohol, and acetic acid respectively. New and even cheaper methods of producing the last two have been discovered. The importance of acetaldehyde lies in the fact that from it a great variety of compounds may be prepared. We will postpone a discussion of this development until the next chapter.

**Formaldehyde.** This aldehyde is prepared by the oxidation of methyl alcohol by air in the presence of metallic silver or copper at a temperature of about  $300^\circ$ . The reaction is carried out on a large scale by passing a mixture of the vapors of methyl alcohol and air through a tube containing copper gauze kept at the desired temperature. The issuing gases containing formaldehyde, water, and unchanged methyl alcohol are passed through water which dissolves the organic material. A forty per cent water solution of formaldehyde is sold as **formalin**.

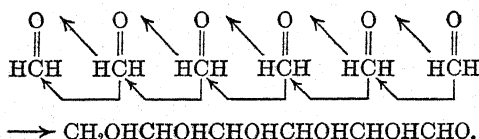
Large quantities of formaldehyde are prepared industrially for use as an antiseptic, as a starting point for the manufacture of other organic compounds, and for the preparation of synthetic resins (p. 354). Formaldehyde solutions are used in preserving and hardening biological specimens. **Paraformaldehyde** (the polymer) is often used as a convenient source of the gas. Such solid paraformaldehyde is often heated in a little burner in order to disinfect a sick room from contagious disease. Formaldehyde gas has a certain disinfecting action and kills the lower forms of life. This is one of the important uses of formaldehyde.

**Unique Properties of Formaldehyde.** As the first member of the series, formaldehyde has certain peculiarities. It differs from the other aldehydes in that on warming with concentrated sodium hydroxide it yields no resin, but undergoes the following peculiar reaction in which one molecule is oxidized at the expense of the other:



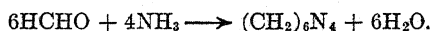
This reaction is known as the **Cannizzaro**<sup>1</sup> reaction; it is characteristic of those *aldehydes which have no hydrogen in the alpha position*, as  $R_3CCHO$ .

When a formaldehyde solution is kept slightly alkaline and allowed to stand, a condensation peculiar to formaldehyde takes place. A mixture of compounds known as sugars (carbohydrates) is formed. These are polyhydroxyaldehydes and ketones and contain five and six carbon atoms in a straight chain (Chap. XVII). The actual product of the self condensation of formaldehyde is a complex mixture, but the reaction may be illustrated by the following equation:



A similar reaction is believed by many to be involved in the formation of carbohydrates in green plants from carbon dioxide and water under the influence of sunlight (Chap. XXXII).

**Hexamethylene tetramine**,  $(\text{CH}_2)_6\text{N}_4$ , is a complex substance obtained by evaporating a mixture of an aqueous solution of formaldehyde and ammonia:



The compound is a crystalline solid which is used in medicine under the name **urotropine**.

**Acetone.** Acetone is the one ketone commonly met. Until 1927, it was prepared by the destructive distillation of calcium acetate which was obtained from the destructive distillation of wood (p. 15).

It is now largely prepared by a special type of fermentation, and is a by-product of the butyl alcohol industry (p. 19). A large amount of acetone is also made by the oxidation of isopropyl alcohol, which, as previously pointed out, is obtained as a by-product of the petroleum industry (p. 67).

The chief use of acetone industrially is as a solvent, since it

<sup>1</sup> Stanislao Cannizzaro (1826-1910), Professor of Chemistry in Rome. In addition to his work in organic chemistry, he played an important part in establishing clear ideas about atomic and molecular weights (1858).

dissolves many organic substances which dissolve even in alcohol with difficulty. The rapid growth of acetone as a commercial solvent may be illustrated by the fact that while 13 million pounds of acetone were manufactured during 1927, over 94 million were produced during 1936.

#### A COMPARISON OF ALDEHYDES AND KETONES

The following table summarizes the more important reactions of aldehydes and ketones. Formaldehyde is given a separate place, since as the first member of the series it has no alkyl group attached to the carbonyl group and has certain unique properties.

	FEHLING'S SOLUTION	FUCHSINE TEST	NaHSO <sub>3</sub>	RMgX YIELDS	
Formal- dehyde	oxidized	positive	addition product	primary alcohol	polymers of high mol. wt.
Acetalde- hyde and other aldehydes	oxidized	positive	addition product	second- ary alcohol	tri- molec- ular polymers
Acetone and other ketones	no action	negative	addition product if CH <sub>3</sub> COR	tertiary alcohol	no polymer

#### QUESTIONS AND PROBLEMS

1. Write structural formulas for: di-*n*-propyl ketone, isopropyl ethyl ketone, propionaldehyde, the bisulfite addition compound of isobutyraldehyde, aldol, the dimethyl acetal of formaldehyde.
2. Write balanced equations for the following reactions indicating the conditions under which the reaction proceeds rapidly: (a) the preparation of acetaldehyde from acetic acid; (b) the commercial method of preparing formaldehyde; (c) a general method of preparing ketones from secondary alcohols; (d) a general method of preparing ketones from acids.
3. By what chemical tests could you distinguish between the following four gases: formaldehyde, methyl chloride, acetylene, ethylene?
4. Compare the physical and chemical properties of formaldehyde, acetone, acetaldehyde and diethyl ketone.

5. Write equations showing the action of ethyl magnesium bromide on: (a) water; (b) formaldehyde; (c) diisopropyl ketone; (d) propionaldehyde. Name the products formed in each case.

6. Outline a procedure for separating by chemical means a mixture of acetone and diethyl ketone.

7. How can acetaldehyde be prepared from paraldehyde? Explain carefully the reaction which is involved and the importance of the conditions.

8. Outline briefly the industrial methods of preparing acetone and formaldehyde. What are the important uses of these compounds?

9. How could you most readily decide whether a given liquid was an alcohol, an aldehyde, a ketone or an acid? What crystalline solids can be readily prepared from aldehydes and ketones and used for purposes of identification? Write equations for the reactions involved in their preparation.

10. Outline methods of preparing the following compounds using as starting material any inorganic reagent and only organic reagents having no more than two carbon atoms: (a) propionaldehyde; (b) diethyl ketone; (c) pinacol; (d) ethyl-dimethyl-carbinol.

11. Show by equations the conversions of the following: (a)  $\text{CH}_3\text{CH}_2\text{OH}$  to  $\text{CH}_3\text{CH}_2\text{COCH}_3$ ; (b)  $\text{CH}_3\text{CH}_2\text{OH}$  to  $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ ; (c)  $\text{CH}_3\text{CH}_2\text{OH}$  to  $\text{CHI}_3$ ; (d)  $\text{CH}_3\text{CH}_2\text{COOH}$  to  $\text{CH}_3\text{CH}_2\text{COCH}_3$ .

12. How would you differentiate between acetaldehyde, diethyl ketone, acetone, and propionaldehyde?

13. Write structural formulas for: propanal; hexanone-3; 2, 2-dimethylheptanal; 4-methyloctanone-3; the semicarbazone of butanone-2.

14. Write equations representing the following reactions: (a) acetonitrile and methyl magnesium iodide followed by treatment with dilute acid; (b) trimethylacetaldehyde and alkali; (c) acetone, bromine, and aqueous sodium hydroxide; (d) diethyl ketone and hydroxylamine.

15. Define the following: (a) Cannizzaro reaction; (b) aldol condensation; (c) haloform reaction; (d) polyoxymethylene; (e) Fehling's solution; (f) paraformaldehyde.

## CHAPTER VII

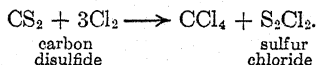
### THE POLYHALOGEN COMPOUNDS: DETERMINATION OF STRUCTURE AND SYNTHESIS OF SIMPLE COMPOUNDS

The polyhalogen derivatives of methane are listed below together with their physical properties. They are all heavier than water and insoluble in it. We shall study in detail a few of the more important polyhalogen compounds.

POLYHALOGEN DERIVATIVES OF METHANE

NAME	FORMULA	MELTING POINT	BOIL- ING POINT
Methylenechloride (dichloromethane)	$\text{CH}_2\text{Cl}_2$	$-97^\circ$	$40^\circ$
Chloroform (trichloromethane)	$\text{CHCl}_3$	$-63^\circ$	$61^\circ$
Carbon tetrachloride	$\text{CCl}_4$	$-23^\circ$	$77^\circ$
Methylenebromide) (dibromomethane)	$\text{CH}_2\text{Br}_2$	$-53^\circ$	$99^\circ$
Bromoform	$\text{CHBr}_3$	$8^\circ$	$151^\circ$
Carbon tetrabromide	$\text{CBr}_4$	$91^\circ$	$190^\circ$
Methyleneiodide (diiodomethane)	$\text{CH}_2\text{I}_2$	$6^\circ$	$181^\circ$
Iodoform	$\text{CHI}_3$	$119^\circ$	
Carbon tetraiodide	$\text{CI}_4$	Sublimes between $90^\circ$ and $100^\circ$ <i>in vacuo</i>	

**Carbon Tetrachloride.** Carbon tetrachloride (tetrachloromethane) is prepared commercially in enormous quantities by the action of chlorine on carbon disulfide which in turn is prepared in the electric furnace by heating coke and sulfur.

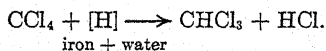


The two products of the chlorination of carbon disulfide can be separated by fractional distillation.

**Uses of Carbon Tetrachloride.** Carbon tetrachloride is a volatile liquid which finds wide use because of its property of being an excellent solvent and because of its incombustibility.

It is one of the few organic substances which will not burn. Being heavier than water and insoluble in water, it can be used for extracting organic compounds from aqueous solution. It is now widely used in the dry cleaning of clothes; for this purpose it is often mixed with gasoline in such proportions that the mixture will not catch fire. Carbon tetrachloride is used in certain types of fire-extinguishers which are particularly adapted for fires which occur in chemical laboratories or in connection with burning oil. When water is poured on oil fires, it tends to spread a layer of burning oil. Carbon tetrachloride, on the other hand, volatilizes; the heavy gas hangs as a smothering cloud over the fire and extinguishes it. Carbon tetrachloride is used in the treatment of animals suffering from internal parasites.

**Preparation of Chloroform.** Chloroform (trichloromethane) can be prepared by reducing carbon tetrachloride with iron and water:



The older method of manufacture consists in distilling ethyl alcohol or acetone with sodium hypochlorite ( $\text{NaOCl}$ ) solution or a suspension of bleaching powder (p. 126).

**Uses of Chloroform.** Chloroform like carbon tetrachloride is non-inflammable and an excellent solvent and, although expensive, is used in the laboratory and in the industries for this purpose. It is also used to a limited extent as an anesthetic. For this purpose it must be pure and kept in completely filled brown bottles, since in the presence of light and air it undergoes decomposition to some extent, forming the poisonous carbonyl chloride  $\text{COCl}_2$  (p. 246) and hydrochloric acid. Commercial chloroform always contains a small amount of ethyl alcohol which in some way prevents the formation of carbonyl chloride.

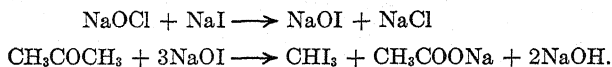
**Chemical Reactions of Chloroform.** On hydrolysis with alkali, chloroform yields formic acid; the "ortho acid,"  $\text{CH}(\text{OH})_3$ , which is perhaps formed first, is not stable (p. 101):



It will be recalled, however, that the esters of orthoformic acid are stable (p. 101); these result when chloroform is treated with a sodium alcoholate. For example, sodium ethylate yields the ethyl ester of orthoformic acid:

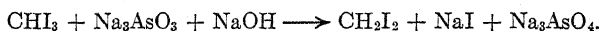


**Iodoform.** Iodoform is prepared from acetone and sodium hypoiodite. Since the latter substance is extremely unstable, it is made as it is needed from sodium iodide and sodium hypochlorite:



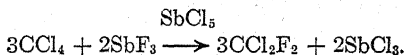
Iodoform is a yellow solid melting at  $120^\circ$  with a characteristic odor. It was used in the early development of antiseptic surgery as a dressing for wounds and is still used to some extent for this purpose.

**Methylene Iodide.** Diiodomethane, usually known as methylene iodide, is prepared by the reduction of iodoform. The best reagent for this purpose is sodium arsenite; this is a rather unusual reducing agent in organic chemistry but is excellent in this particular instance, the yield being almost quantitative:



Methylene iodide is a colorless liquid boiling at  $181^\circ$  and having a density of 3.3. With the exception of mercury it is the heaviest liquid known.

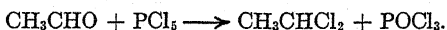
**Dichlorodifluoromethane.** The only fluorine derivative of paraffin hydrocarbons having industrial importance is dichlorodifluoromethane,  $\text{CCl}_2\text{F}_2$ , a gas which boils at  $-30^\circ$ . The commercial significance of this substance lies in the fact that it is an ideal refrigerant. For refrigerators and for air conditioning units, it is far superior to ammonia, sulfur dioxide, and ethyl chloride in that it is practically odorless, non-toxic, non-inflammable, and non-corrosive. Dichlorodifluoromethane is manufactured from carbon tetrachloride by a rather special process:



#### HALOGEN DERIVATIVES OF ETHANE AND OTHER HYDROCARBONS

**Isomeric Dichloroethanes.** The two isomeric dichloroethanes, ethylene dichloride,  $\text{CH}_2\text{ClCH}_2\text{Cl}$ , and ethylidene chloride,  $\text{CH}_3\text{-CHCl}_2$ , were mentioned in the last chapter in connection with the structures of ethylene and acetaldehyde (p. 127). The former is

prepared from ethylene and chlorine (p. 58) and is produced industrially for use as a solvent. It is a liquid, insoluble in water and boiling at 84°. The isomeric chloride (b.p. 59°) results from the action of phosphorus pentachloride on acetaldehyde:



**Dibromoethanes.** Ethylene dibromide,  $\text{CH}_2\text{BrCH}_2\text{Br}$  (b.p. 131°), is prepared by the action of bromine on ethylene (p. 58), while its isomer (b.p. 113°) is prepared either by the action of phosphorus pentabromide on acetaldehyde or by the addition of hydrobromic acid to acetylene:

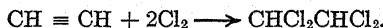


**Tetrachloroethylene.** Tetrachloroethylene is obtained as a by-product of the manufacture of chloroform from carbon tetrachloride:



It is a liquid which boils at 121°. It is finding use in place of carbon tetrachloride in the treatment of internal parasites in animals.

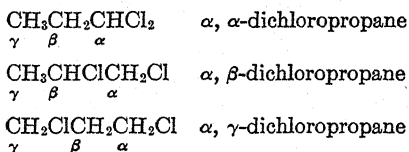
**Acetylene Tetrachloride.** This substance is prepared by the action of chlorine on acetylene:



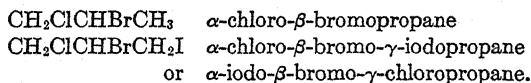
The reaction is almost explosive unless the gases are brought together in the presence of some inert solid material. Acetylene tetrachloride (symmetrical tetrachloroethane) is a liquid which boils at 147°. It is a valuable solvent for cellulose acetate (p. 321) and other organic compounds.

**Nomenclature of Polyhalogen Compounds.** A general method of naming the halogen derivatives of the hydrocarbons is necessary, since the higher members of the series have many isomers. Thus, while trichloromethane can only mean  $\text{CHCl}_3$  (chloroform), trichloropropane might be any one of five isomers. The method commonly employed is to consider the substances as derivatives of the corresponding paraffin hydrocarbon and to denote by Greek letters the position of the substituting atoms. The number, name, and position of the halogen atoms come first, and the

name of the parent hydrocarbon last. The following examples will make this clear:



The Greek letters are written under the above formulas to indicate the method; they are usually written only in the name. The lettering should always begin from the most substituted end of the molecule (which, of course, may be either at the right or the left depending on how the formula is written). The method of naming compounds with different halogen atoms is shown below:



The Geneva method of naming the polyhalogen compounds is now preferred by many people. The compounds are named from the longest straight chain paraffin hydrocarbon, and the position of the substituent halogen atoms indicated by numerals in the usual way. Thus  $\text{CH}_3\text{CH}_2\text{CHCl}_2$  is 1,1-dichloropropane,  $\text{CH}_3\text{CHCHClCHBrCH}_3$ , is 2-methyl-3-chloro-4-bromopentane,

$\begin{array}{c} | \\ \text{CH}_3 \end{array}$   
 and  $\text{CH}_2\text{ClCH}_2\text{CH}_2\text{CHClCH}_3$ , is 1, 4-dichloropentane.

**General Methods of Preparing Polyhalogen Compounds.** The halogen derivatives of methane and ethane which have just been discussed are peculiar in that the halogen atoms must be on the same or on adjacent carbon atoms. With compounds containing many carbon atoms we have a great variety of halogen compounds. These substances are often very useful in organic syntheses, since they will enter into many metathetical reactions. Irrespective of the length of the carbon chain we may summarize the methods of preparing dichloro and dibromo compounds as follows:

(a) *Two halogen atoms on same carbon atom*: Such compounds are prepared from aldehydes or ketones by the action of phosphorus pentachloride or pentabromide.

(b) *Two halogen atoms on adjacent carbon atoms:* Compounds formed by the addition of chlorine or bromine to an olefin.

(c) *Two halogen atoms on carbon atoms removed by one or more carbon atoms:* These compounds are prepared from the corresponding hydroxy compounds (Chap. IX) by reactions exactly similar to those used in preparing alkyl halides from alcohols.

#### DETERMINATION OF STRUCTURE AND SYNTHESIS OF SIMPLE COMPOUNDS

In the previous chapters we have considered a variety of organic compounds and discussed methods for their preparation and some of their typical reactions. Such information is part of the working knowledge of every organic chemist. By means of it he is able to determine the structure of new compounds which may be discovered and to outline a procedure for their synthesis. The actual problems which are confronting the investigator today are too complex, for the most part, to be considered in the first course in the subject. The methods used in attacking these problems, however, are exactly like those employed in determining the structure of simple compounds. Indeed, occasionally some new, but relatively simple compound is found or prepared even today and some of the examples considered in the following pages are taken from research work.

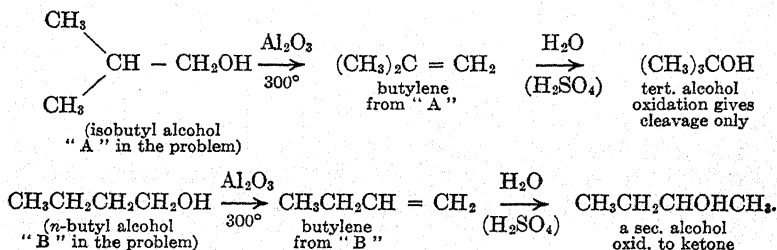
In general there are two ways of determining the structure of an unknown compound. We may study its reactions and break it down by a variety of methods or we may attempt to synthesize it by known reactions. Usually both methods are employed in such a way as to reinforce each other. Specific problems concerning different classes of compounds will illustrate these methods and at the same time provide a review of the material of the last six chapters.

Let us first consider the subject of alcohols. If a certain pure substance by analysis and molecular weight determination corresponds to the general formula  $C_nH_{2n+1}OH$ , reacts with phosphorus trichloride and is esterified by acids, we may conclude that it is an alcohol. The problem next arises as to what particular alcohol it may be. If the substance is known, we can of course examine its physical properties and, by comparing these with those of the known compound, identify the material. If it has never before been prepared, then a real problem confronts us.

**Is an Alcohol Primary, Secondary, or Tertiary?** Suppose the alcohol in question is  $C_4H_9OH$  and that we are the first discoverers of any one of the possible isomers. The first thing to do is to determine whether it is a primary, a secondary or a tertiary alcohol. This is done by oxidation. The products are obtained in a pure state and analyzed. If our compound yields in this way an acid  $C_3H_7COOH$ , it must have been a primary alcohol. If it yields  $CH_3COOH$  or  $C_2H_5COOH$  (acids with fewer atoms), we must try to isolate an intermediate product. If we can isolate a ketone  $C_4H_8O$ , then we know that the substance must be a secondary alcohol. If no such compound is formed, we must conclude that the substance is a tertiary alcohol.

Such *class reactions* enable us to reduce greatly the number of possibilities. Except in the case of very simple compounds they are insufficient to solve the problem, however. The possibilities can be still further decreased by studying the transformation and degradation to simpler molecules. In the case of alcohols or alkyl halides it is often useful, for example, to transform them into the corresponding olefins (p. 60). If we can determine the structure of the resulting olefin, the structure of the alcohol may become evident.

**The Structure of Butyl and Isobutyl Alcohol.** There are two primary alcohols with the formula  $C_4H_9OH$  which we will call A and B. On dehydration with a catalyst (p. 60) they form two isomeric butylenes,  $C_4H_8$ , which in turn combine with water (in the presence of acids, p. 67), to yield alcohols,  $C_4H_9OH$ . The butylene from "A" yields tertiary butyl alcohol,  $(CH_3)_3COH$  (the only possible tertiary alcohol,  $C_4H_9OH$ ); the other yields the secondary alcohol,  $CH_3CH_2CHOHCH_3$ . From these facts, it is clear that A must be isobutyl alcohol,  $(CH_3)_2CHCH_2OH$ , and B normal butyl alcohol.



**Dehydration of Alcohols.** In the laboratory it is frequently more convenient to dehydrate an alcohol by heating it with a small amount of sulfuric acid to a temperature at which water distills from the reaction mixture. In place of sulfuric acid, strong organic acids may be used as catalysts. This method is particularly adapted to the dehydration of secondary and tertiary alcohols.

**Structure of Olefins.** In the example just given the structure of two olefins was determined by converting them into alcohols by combining them with water (note the importance of Markownikoff's rule, p. 65) and determining the nature of the alcohol. A more general method of determining the structure of olefins is by oxidation. For this purpose ozone is the best reagent and is superior to potassium permanganate which has been used, however (p. 66). A stream of oxygen containing from 3-6 per cent

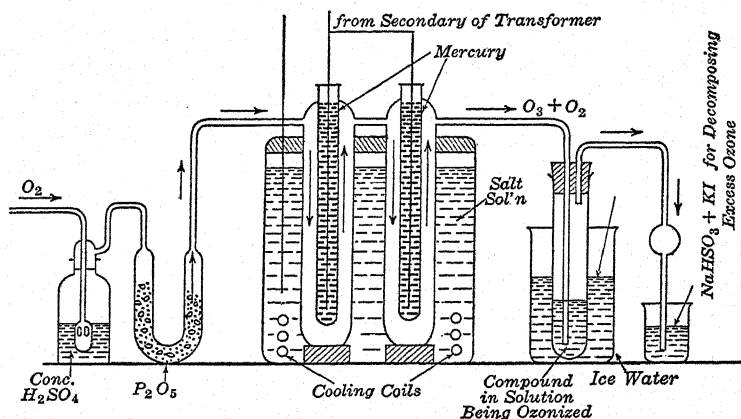
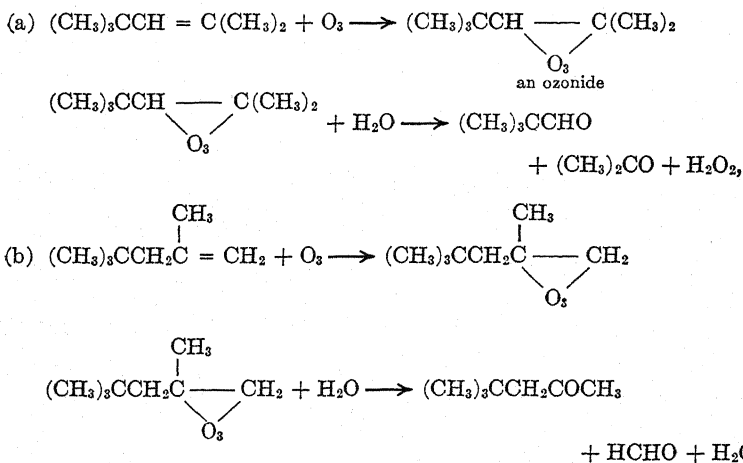


Fig. 19. Apparatus used in the laboratory for treating unsaturated compounds with ozone.

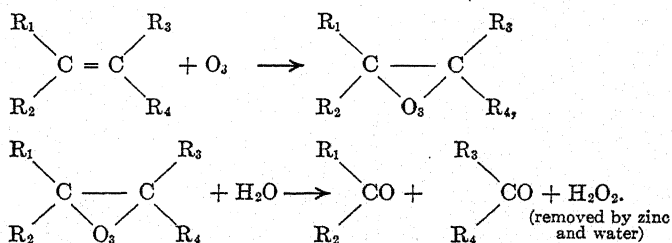
ozone (obtained by passing a silent electric discharge through oxygen) is bubbled through the unsaturated hydrocarbon (Fig. 19). The ozone rapidly combines with the unsaturated compound, forming a substance known as an **ozonide**. The resulting addition product on decomposition with water yields a mixture of **aldehydes or ketones** and hydrogen peroxide. The latter must be destroyed by the use of some mild reducing agent (*e.g.*, zinc and water) as otherwise it will oxidize any aldehyde to an acid. The aldehydes and ketones can be identified if they are known, other-

wise their structure may be determined by methods similar to those we have considered.

The following equations illustrate the behavior of two isomeric octenes when ozonized. It will be noted that the products (after decomposing the ozonide with water) are different in each case:



The equations written above illustrate two specific cases. A general equation summarizing the method is as follows, in which  $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4$ , may be alkyl groups or hydrogen atoms:



**Proof of Structure by Synthesis.** The final proof of the correctness of a structural formula is the synthesis of the compound by known steps. A careful comparison of the physical and chemical properties of the compound under examination with those of the synthetic product will establish whether or not the two materials are identical. If the reactions and transformations of the un-

known compound enable one to state definitely that it is one of two or three possibilities, it is often easiest to complete the solution of the problem by synthesis. Samples of each of the possibilities are prepared and compared with the unknown. This is the only method which can be employed in some cases. This is particularly true of the paraffin hydrocarbons which are not readily transformed into other compounds and have no characteristic reactions.

The problem of determining the structure thus often becomes a problem of synthesis. Synthetic problems also arise for other reasons. New compounds may be desired in order to test their physiological action, to study some physical or chemical property, or to test some possible commercial use.

#### SYNTHETIC PROBLEMS IN THE LABORATORY

The organic chemist is thus often faced with the problem of preparing a certain substance in the laboratory. He must first decide what method is to be employed. As a preliminary step he usually outlines a possible method and then goes to the library to consult the work of other investigators in this same field to see what information he can obtain. Very frequently little or nothing has been published on his particular problem and he must try out the proposed scheme for the first time himself. We shall outline the general way in which chemists solve such synthetic problems.

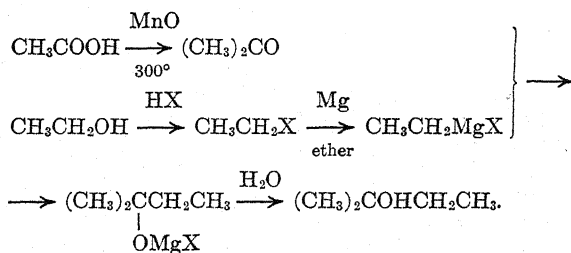
**Synthesis of a Carbinol.** Suppose the study of a compound  $C_5H_{11}OH$  has led us to believe that it is dimethylethylcarbinol  $(CH_3)_2COHC_2H_5$ . How is a sample of this compound to be made for purposes of comparison?

**Steps in Solving a Synthetic Problem.** The first step is to write the structural formula. The second is to recall the methods available for preparing tertiary alcohols. The action of a Grignard reagent on a ketone comes to mind:



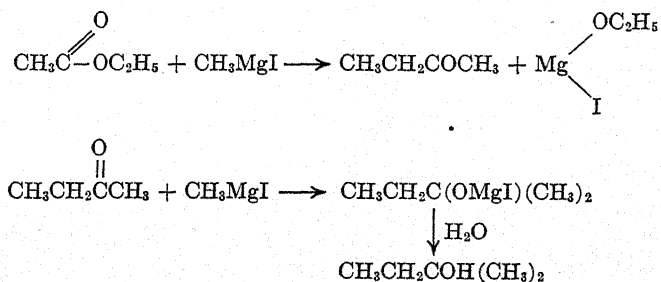
What Grignard reagent, what ketone? A consideration of the formula for dimethylethylcarbinol  $(CH_3)_2COHC_2H_5$  soon shows that the Grignard reagent could be ethyl magnesium bromide  $C_2H_5MgBr$ , the ketone, acetone  $CH_3COCH_3$ .

Even the beginner in organic chemistry is now on familiar ground. Ethyl magnesium bromide can be prepared from ethyl bromide which in turn is made from ethyl alcohol. Acetone, if not available, could be prepared from acetic acid by the catalytic process. If we imagine that circumstances force the chemist to start with such simple substances as acetic acid, ethyl alcohol, and inorganic material, the steps in the synthesis may be represented as follows:



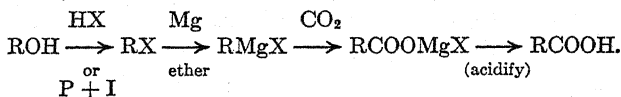
It often happens that there is more than one possible route to the desired goal, but usually one route is shorter and better than the others. In the example above we might have elected to treat methyl ethyl ketone with methyl magnesium iodide; methyl ethyl ketone, however, being a mixed ketone, is less readily prepared than acetone.

**Tertiary Alcohols from Esters.** In addition to the method previously given for preparing tertiary alcohols, it will be well to mention another useful method. This consists in treating an ester with a Grignard reagent (a ketone is formed as an intermediate but rarely can be isolated). The method is illustrated by the preparation of dimethylethylcarbinol from ethyl propionate and two moles of methyl magnesium iodide.

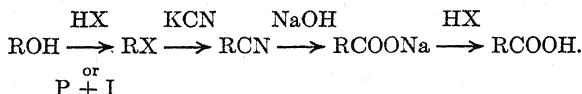




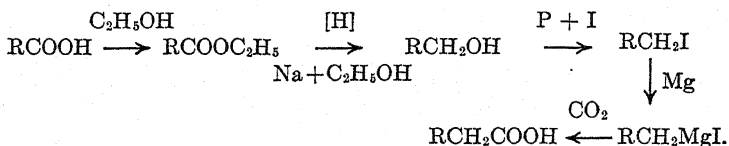
*Problem: Synthesize an acid RCOOH from an alcohol ROH.*



*Alternative method (less satisfactory in some cases).*



*Problem: Synthesize an acid RCH<sub>2</sub>COOH from an acid RCOOH.*



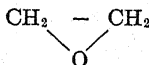
*Alternative for last two steps, prepare RCH<sub>2</sub>CN and hydrolyze.*

These syntheses make use of many of the reactions treated in the earlier chapters. They are tabulated here for ready reference. The student is advised not to attempt to memorize such schemes but rather to understand the method of working out synthetic problems backward, step by step. He should have at his fingertips a few methods of preparing each type of compound considered up to this point.

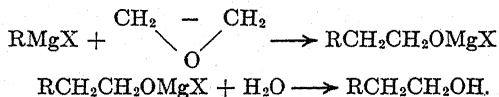
**Limitations of the Reactions.** These synthetic methods which we have generalized above by the use of the symbol R for an alkyl group, are subjected to serious limitations in practice. A consideration of these limitations is the province of an advanced course in organic chemistry. As an example of such limitations, we may mention the fact that certain highly branched ketones, such as (CH<sub>3</sub>)<sub>3</sub>CCOC(CH<sub>3</sub>)<sub>3</sub>, will not react with the Grignard reagent, or react abnormally. In general, the *branching of the chain* near the functional group and the introduction of reactive groups (halogen, OH, NH<sub>2</sub>, etc.) modify the reactions greatly. Increasing the length of the chain as a rule has little disturbing influence; hence the general methods of synthesis give good results in all cases where primary alkyl groups are attached to the reacting group.

**Adding Two Carbon Atoms to the Chain.** We have already considered methods of lengthening a carbon chain, one atom at a time. If we wish to prepare *n*-hexyl alcohol from *n*-butyl alcohol,

it would be possible first to synthesize *n*-amyl alcohol and then repeat the steps, using this new alcohol as the starting point. A much more convenient method of adding two carbon atoms is to treat the Grignard reagent with ethylene oxide.



The reaction is carried out by passing the gas into the Grignard reagent in ether and decomposing the mixture in the usual way:



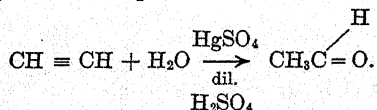
Ethylene oxide is a gas at room temperature (b.p. 13°); it is discussed in detail on page 173.

#### THE SYNTHESIS OF ORGANIC COMPOUNDS FROM CALCIUM CARBIDE

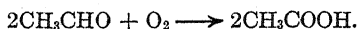
Calcium carbide is prepared by heating lime and coal in an electric furnace. On treatment with water it yields acetylene. This reactive hydrocarbon is, therefore, a cheap raw material where hydroelectric power is available, and in recent years has supplied a large chemical industry. Acetylene is first converted into acetaldehyde; from this a host of useful substances may be prepared. Since these transformations represent the synthesis of a variety of simple compounds they will be considered in this chapter.

**Acetaldehyde from Acetylene.** Acetaldehyde is prepared by passing acetylene into a vigorously agitated suspension of mercuric sulfate in dilute sulfuric acid. The temperature of the reaction mixture is somewhat above room temperature, and the acetaldehyde (b.p. 20°) distills as rapidly as it is formed. By suitable condensers and fractionating columns it can be separated from the excess of acetylene and obtained very pure.

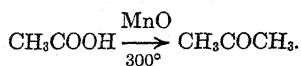
An examination of the formulas of acetylene and acetaldehyde makes it evident that the formation of one from the other involves the addition of a molecule of water. There are several steps in the actual reaction, and both the acid and the mercuric sulfate are catalysts for the process:



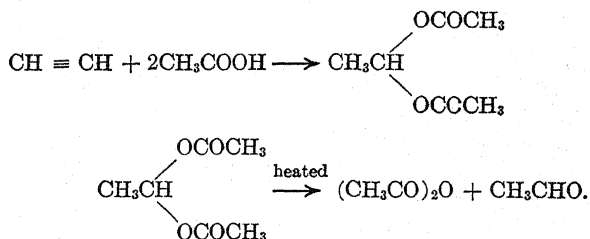
**Acetic Acid, Acetone, and Acetic Anhydride from Acetylene.** Acetaldehyde can be oxidized by the air to acetic acid: in this way this important raw material is indirectly synthesized from calcium carbide. One method of carrying out the oxidation is to mix the aldehyde with some acetic acid and suspend certain metallic oxides in the solution. When air is blown through this mixture, the aldehyde is converted into the acid:



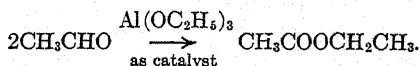
If acetic acid vapors are passed over a hot metallic oxide, acetone is formed (p. 109):



If acetylene is passed into acetic acid containing a metallic catalyst, a compound, ethylidene diacetate,  $\text{CH}_3\text{CH}(\text{OCOCH}_3)_2$ , is produced. This compound on heating yields acetic anhydride and acetaldehyde. The latter is used for the production of acetic acid:

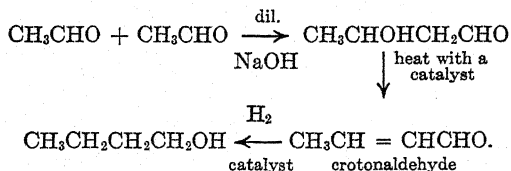


**Production of Ethyl Acetate.** Still other products may be made from the very reactive substance, acetaldehyde. In the presence of aluminum ethylate,  $\text{Al}(\text{OC}_2\text{H}_5)_3$  (made by the action of aluminum amalgam on ethyl alcohol), acetaldehyde undergoes a peculiar change in which ethyl acetate is the product:



Ethyl acetate is valuable as a solvent and to some extent is manufactured in this way.

**Synthetic Butanol.** By means of the aldol condensation an unsaturated aldehyde (crotonaldehyde) can be formed from acetaldehyde. Subsequent catalytic reduction of this yields synthetic normal butyl alcohol. The reactions are outlined below:



It is claimed that butyl alcohol can be prepared as cheaply by this series of reactions as by the fermentation process.

The preparation of ethyl alcohol from calcium carbide by the steps, — acetylene, acetaldehyde, ethyl alcohol, is said to have been carried out industrially in Europe. The catalytic hydrogenation of acetaldehyde presents no difficulties; it seems unlikely, however, that this synthetic method will replace the fermentation process.

### QUESTIONS AND PROBLEMS

1. Write structural formulas for: (a)  $\alpha$ ,  $\beta$ -dichlorobutane; (b)  $\alpha$ -bromo- $\gamma$ -chloro-propane; (c)  $\beta$ ,  $\beta$ -dichloropropane; (d)  $\alpha$ ,  $\beta$ ,  $\gamma$ -tribromopentane, 1, 2, 4-tribromopentane, 2-methyl-3, 3-dichlorobutane, 1, 5-diiodohexane.

2. Name the following by two methods:  $\text{CHCl}_2\text{CH}_2\text{CH}_2\text{Br}$ ;  $\text{CH}_2\text{BrCHClCH}_3$ ;  $\text{CH}_3\text{CHCl}_2$ ;  $\text{CH}_3\text{CHClCH}_2\text{Br}$ .

3. Write equations for the steps involved in the preparation of: (a) chloroform from ethyl alcohol; (b) iodoform from acetone; (c) chloroform from carbon disulfide.

4. By what reactions is it possible to prepare the following from *n*-propyl alcohol:  $\alpha$ ,  $\beta$ -dibromopropane (propylene dibromide);  $\alpha$ ,  $\alpha$ -dibromopropane?

5. What products would you expect to obtain by warming methyl ethyl ketone with sodium hypochlorite solution? By warming acetaldehyde with sodium hypobromite?

6. By what reactions (or series of reactions) could one decide whether a certain compound was  $\text{CH}_3\text{CHOHCH}_2\text{CH}_3$ ;  $(\text{CH}_3)_2\text{CHCH}_2\text{OH}$ ; or  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ ?

7. Show how it would be possible to determine the structure of an aldehyde which had the formula  $\text{C}_4\text{H}_8\text{O}$ . (Hint: Write all possible formulas *first*.)

8. A compound  $\text{C}_4\text{H}_8$  reacts with bromine forming a compound  $\text{C}_4\text{H}_8\text{Br}_2$ . Write all possible formulas for the hydrocarbon and suggest methods of determining which formula corresponds to the compound at hand. (Assume that the isomeric substances  $\text{C}_4\text{H}_8$  are unknown, and the unknown can not be identified, therefore, by means of its physical constants.)

9. Write equations for the reactions involved in the preparation of isopropyl alcohol from calcium carbide.

10. Show the steps involved in the synthesis of: (a) *n*-amyl alcohol from *n*-butyl alcohol; (b) triethylcarbinol from ethyl alcohol; (c) diethyl ketone from ethyl alcohol.

11. Given acetic acid, methyl and ethyl alcohols, ether, and inorganic reagents, show how you might prepare: (a) trimethylcarbinol; (b) ethyl propionate; (c) propylene dibromide; (d) dimethyl-ethyl-carbinol.

12. Outline the steps in the preparation of the following from materials which you know are available in your laboratory: (a)  $(\text{CH}_3)_2\text{CBrCH}_2\text{Br}$ ; (b)  $(\text{CH}_3\text{CH}_2)_2\text{ClCH}_3$ ; (c)  $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)_2$ ; (d)  $(\text{CH}_3)_2\text{CHCHOHCH}(\text{CH}_3)_2$ ; (e)  $\text{CH}_3\text{CH}_2\text{CHBrCH}_2\text{CH}_3$ .

13. If an industrial plant had as by-products large amounts of carbon monoxide, propylene, hydrogen, and ethylene, what alcohols could be prepared without purchasing other organic material? What esters? Outline the steps in the synthesis of these products and any others which seem to you possible.

14. The following substances are used in considerable amounts in the industries: acetone, ethylene chloride, ethyl acetate, acetic anhydride, ethyl chloride, butyl acetate. Outline a scheme for preparing all these compounds cheaply at a location where there is hydroelectric power.

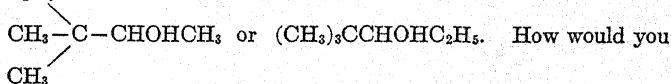
15. Illustrate with equations the steps involved in the following conversions: (a)  $\text{C}_2\text{H}_5\text{CHO}$  to  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_3$ ; (b)  $\text{CH}_3\text{COOCH}_3$  to  $\text{CH}_3(\text{C}_2\text{H}_5)_2\text{COH}$ ;

(c)  $\text{C}_2\text{H}_5\text{OH}$  to *n*- $\text{C}_3\text{H}_7\text{OH}$ ; (d)  $\text{CH}_3\text{OH}$  to *n*- $\text{C}_3\text{H}_7\text{OH}$ ; (e)  $\text{C}_2\text{H}_5\text{OH}$  to  $\text{CH}_3\text{CHOHCH}_3$ ; (f)  $\text{C}_2\text{H}_5\text{COOH}$  to  $\text{C}_3\text{H}_7\text{COOH}$ .

16. A compound A has an empirical formula  $\text{C}_5\text{H}_{10}\text{O}$ . With  $\text{CH}_3\text{MgI}$  it liberates 1 mol of methane. On oxidation it loses two hydrogen atoms and gives a compound which forms an oxime. When the oxidation product is treated with an alkaline solution of iodine there is formed iodoform and isobutyric acid. What is the structure of A?

17. A hydrocarbon ( $\text{C}_6\text{H}_{10}$ ) on hydrogenation gives 2-methyl-butane. When treated with conc.  $\text{H}_2\text{SO}_4$  and then with water an alcohol is obtained, which on oxidation gives a ketone. What is the structure of the original hydrocarbon?

18. A compound was isolated from a reaction; its structure is to be represented by  $\text{C}_2\text{H}_5$



How would you proceed to prove which of these two structures is correct?

## CHAPTER VIII

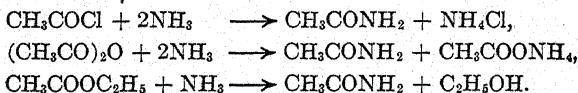
### DERIVATIVES OF AMMONIA: AMIDES, NITRILES, AMINES

A large portion of the preceding chapters has been devoted to compounds which are related to water. Thus, alcohols, ROH, may be regarded as alkyl derivatives of water; ethers, ROR, as dialkyl derivatives; acids,  $RC = O(OH)$ , as acyl derivatives and acid anhydrides as diacyl derivatives  $(RCO)_2O$ . We shall now consider the corresponding nitrogen compounds which are related to ammonia. These are: amines,  $RNH_2$ ,  $R_2NH$ ,  $R_3N$  and amides,  $RCONH_2$ . In these substances, one or more hydrogen atoms of ammonia have been replaced by alkyl or acyl groups. We shall find the differences between water and ammonia reflected in these compounds; the derivatives of water are more acidic, those of ammonia more basic.

#### AMIDES

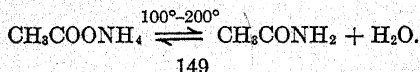
**Preparation of Amides.** Of the acyl derivatives of ammonia only those containing one acyl group are of importance. They are known as the amides,  $RCONH_2$ . The best known is acetamide,

$\begin{array}{c} O \\ || \\ CH_3C - NH_2 \end{array}$ . The following equations represent the typical methods of preparing amides as applied to acetamide:



The first two reactions take place rapidly in most cases; the reaction of esters with ammonia is slow. The parallelism between the action of ammonia (ammonolysis) and water (hydrolysis) is striking. If we substitute water for ammonia in these reactions, an acid is formed.

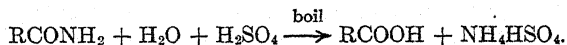
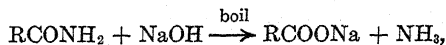
**Amides from Ammonium Salts.** Another convenient method of preparing amides is to heat the ammonium salt of the corresponding acid:



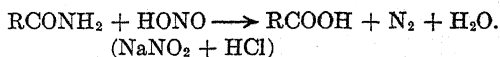
This reaction is reversible; it proceeds at an appreciable rate only at about 100° or higher. If we can remove the water as rapidly as it is formed, the reaction will go to completion in spite of an unfavorable equilibrium. Since the amides are high-boiling and the ammonium salts essentially non-volatile substances, this is easy to accomplish by using a suitable apparatus.

**Hydrolysis of Amides.** The amides are hydrolyzed by boiling a water solution with acid or alkali which catalyzes the reaction. If we add one equivalent of sodium hydroxide, the reaction goes to completion for the same reason that the saponification of esters with alkali is complete (p. 98). With one mole of acid the reaction also goes to an end, since the ammonia is removed as the ammonium salt.

The equations for the reactions are given below:



**Reaction with Nitrous Acid.** When treated with nitrous acid, amides yield nitrogen and the corresponding acid. This reaction, like the hydrolysis of amides, may be used for preparing acids from the corresponding amide. Since nitrous acid is known only in dilute water solutions which slowly decompose, it is prepared by adding hydrochloric acid to an aqueous solution of sodium nitrite:



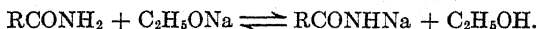
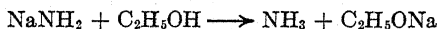
**Physical and Chemical Properties.** The simple amides are very soluble in water and surprisingly high-melting and high-boiling substances, as the following table illustrates:

NAME	FORMULA	BOILING POINT	MELTING POINT
Formamide	HCONH <sub>2</sub>	193°	+2°
Acetamide	CH <sub>3</sub> CONH <sub>2</sub>	222°	81°
Propionamide	CH <sub>3</sub> CH <sub>2</sub> CONH <sub>2</sub>	213°	79°
Butyramide	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CONH <sub>2</sub>	216°	116°

The amides may be regarded as *neutral substances*. Their acidic and basic properties are so weak that they are not mani-

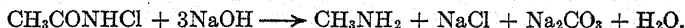
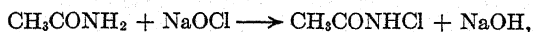
fested in water solution. This is in contrast to the parent compound, ammonia, which is a base. The substitution of an acyl group for hydrogen has greatly decreased the basic properties of the  $\text{NH}_2$  group.

The effect of the acyl group in increasing the acidity of the  $-\text{OH}$  group is apparent from a comparison of acetic acid and water (p. 84). Similarly one might expect that an amide would be a stronger *acid* than ammonia. Indeed, this is the case but even the introduction of one acyl group has not conferred sufficient acidity on the amide,  $\text{RCONH}_2$ , to make it form soluble salts which are stable in water. As far as can be judged by rather approximate methods, acetamide and similar compounds are about as acidic as alcohol; on the other hand, ammonia is definitely a weaker acid than alcohol. Sodamide,  $\text{NaNH}_2$ , the sodium salt of ammonia, is decomposed by water and alcohol; the sodium derivative of acetamide only by water:



We shall see in later chapters that when *two* acyl groups are substituted for the hydrogen atoms of ammonia (p. 206), the resulting compound is distinctly more acidic. The amides of the strong sulfonic acids (p. 351) are acidic enough to form sodium salts which are only slightly hydrolyzed by water.

**The Hofmann Reaction.** The most important reaction of amides is known as the Hofmann<sup>1</sup> reaction: the amide is converted into an alkyl derivative of ammonia, an amine,  $\text{RNH}_2$ . The mechanism of this extraordinary change is complicated and obscure. The first step consists in the replacement of a hydrogen atom by a halogen atom; the resulting compound is rapidly decomposed by alkali with the *elimination of a carbon atom* as carbon dioxide:



The reaction is carried out by treating an aqueous solution of the amide with sodium hypochlorite, or sodium hypobromite and sodium hydroxide. On distilling the mixture, the amine, which is volatile, distills and is collected.

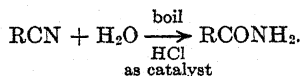
It is evident that the Hofmann reaction amounts to clipping one carbon atom from the end of a carbon chain. For this reason, it has been of importance in preparing simpler compounds.

<sup>1</sup> August Wilhelm von Hofmann (1818-1892), for twenty years Professor at the Royal College of Chemistry, London. From 1865 until his death, Professor at the University of Berlin.

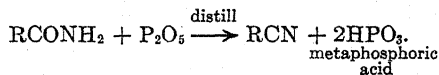
from more complicated ones and in determining the structure of compounds with long carbon chains.

With the higher members of the fatty acid series the reaction proceeds a little farther and an amide  $\text{RCH}_2\text{CONH}_2$ , instead of giving a primary amine,  $\text{RCH}_2\text{NH}_2$ , yields the corresponding nitrile  $\text{RCN}$ . However, from the nitrile we can readily prepare the acid by hydrolysis (p. 89) or the amine by reduction (p. 155).

**Interconversion of Amides and Nitriles.** A nitrile on hydrolysis yields an acid (p. 89). The first step in this process is an amide and under certain conditions the reaction may be stopped at this point.



The reverse of this reaction is accomplished when amides are heated with phosphorus pentoxide. The distillate consists of the more volatile nitrile:

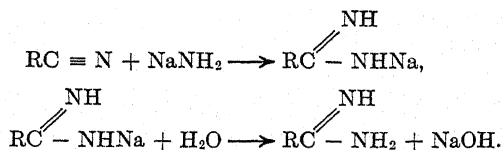


It should be noted that while the hydration (addition of water) of nitriles to amides and the dehydration of amides to nitriles is a process which can be made to go in either direction depending on the reagents employed, it is *not a reversible reaction*. A reversible reaction (as the term is usually employed) is a reaction which, in the presence of a suitable catalyst, comes to an equilibrium point in a relatively short time. In the case of a reversible reaction changing the concentration of reactants and products alters the composition of the equilibrium mixture, and in some cases changing the temperature shifts the equilibrium. In the case of the interconversion of amides and nitriles, while the process may be *reversed* by employing different reagents, no equilibrium is established under the usual laboratory conditions. The hydrolysis (hydration) reaction *runs to completion*. To reverse this reaction it is necessary to employ some dehydrating agent such as phosphorus pentoxide which will remove the elements of water from the amide by a chemical reaction. This process also goes to completion. A comparison of the interconversion of ammonium salts and amides on the one hand (a truly reversible reaction) and

amides and nitriles on the other (not a reversible reaction at usual temperatures) illustrates the significant difference between two closely related types of organic reactions.

**Amidines.** Just as the *hydrolysis* of a nitrile produces an amide, so the *ammonolysis* of a nitrile produces a compound known as an amidine,

$\text{RC} \equiv \text{N}$   $\xrightarrow{\text{NH}_3}$   $\text{RC} = \text{NH}$ . This ammonolysis can be accomplished by heating a nitrile with sodamide, followed by the hydrolysis of the sodium salt of the amidine:



The amidines differ from the amides in being bases which form salts with mineral acids which are stable in water. Thus acetamidine hydrochloride is  $\text{CH}_3\text{C}(=\text{NH})\text{NH}_2 \cdot \text{HCl}$ .

### THE NITRILES

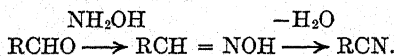
Since nitriles may be regarded as dehydration products of acyl derivatives of ammonia, they may be considered as a class at this point.

**Methods of Preparation.** The nitriles are usually prepared by the interaction of an alkyl halide with sodium or potassium cyanide (p. 26):



It is worth noting that this reaction is satisfactory only if the alkyl halide is one which is derived from a primary or secondary alcohol. With highly branched compounds other inorganic cyanides, such as cuprous cyanide, are more satisfactory.

A second method of preparing nitriles starts with the corresponding aldehyde. This is converted into the oxime, and then the latter is dehydrated with acetic anhydride:



The preparation of nitriles from acids through the amides has just been considered.

**Nomenclature.** The nitriles are usually named from the acid into which they are converted by hydrolysis; thus, *acetonitrile* is  $\text{CH}_3\text{CN}$ , because on hydrolysis this substance yields acetic acid,

$\text{CH}_3\text{COOH}$ . Similarly, we have **propionitrile**,  $\text{CH}_3\text{CH}_2\text{CN}$ . Another method of naming these compounds is to consider them as esters of hydrocyanic acid ( $\text{HCN}$ ). Thus acetonitrile may be called methyl cyanide, and propionitrile, ethyl cyanide.

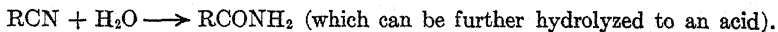
**Physical and Chemical Properties.** The lower nitriles are colorless liquids boiling somewhat lower than the acids into which they can be hydrolyzed. They have neither acidic nor basic properties.

PHYSICAL PROPERTIES OF THE SIMPLE NITRILES

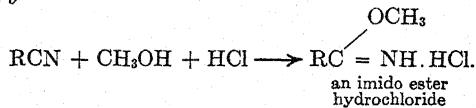
NAME	FORMULA	BOILING POINT
Acetonitrile	$\text{CH}_3\text{CN}$	$81.6^\circ$
Propionitrile	$\text{CH}_3\text{CH}_2\text{CN}$	$98^\circ$
<i>n</i> -Butyronitrile	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$	$118.5^\circ$
Isobutyronitrile	$(\text{CH}_3)_2\text{CHCN}$	$107^\circ$

The triple linkage between carbon and nitrogen is characteristic of a nitrile. It represents an unsaturation somewhat similar to that which occurs in acetylene, and we should expect that the nitriles would combine with two or four atoms or groups. Of course, the reagents which add to a carbon-nitrogen triple bond are often quite different from those which add to a carbon-carbon triple bond. Some of the addition reactions of nitriles have already been mentioned, and these, together with some new reactions, are listed below:

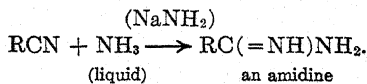
1. *Hydrolysis*:



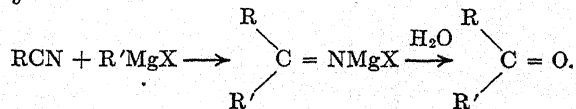
2. *Alcoholysis*:

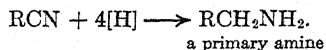
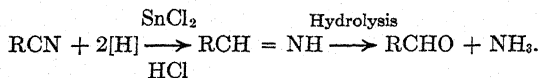


3. *Ammonolysis*:



4. *Grignard Reaction*:



5. *Reduction:*6. *Conversion to Aldehydes:*

(Only this particular reducing agent is employed)

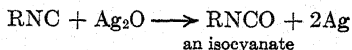
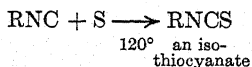
Since the nitrile RCN can be easily made in two steps from the alcohol ROH it will be evident that these reactions give us a method of preparing a number of compounds from a given alcohol.

**Isonitriles.** A class of compounds isomeric with the nitriles are the isonitriles. In these compounds the alkyl group is attached to the nitrogen atom instead of the carbon atom. They are formed together with the nitriles by the interaction of an alkyl halide and a metallic cyanide. If silver cyanide is used the main product is an isonitrile:



The isonitriles are also known as the **carbylamines** or the **alkyl isocyanides**. The lower members of the series are liquids insoluble in water and with boiling points somewhat lower than the isomeric nitriles. They have a peculiarly bad odor.

On hydrolysis the isonitriles yield a primary amine (see below) and formic acid. The carbon atom has the ability to combine with other atoms as illustrated by the reaction of an isocyanide with sulfur or silver oxide.



The structure of the isonitrile group is considered later in this chapter (p. 168).

## AMINES

**Nomenclature.** The amines are the alkyl derivatives of ammonia. They may be divided into the following classes:

- (1) a primary amine,  $\text{RNH}_2$ , *e.g.*,  $\text{CH}_3\text{NH}_2$  methyl amine,
- (2) a secondary amine,  $\text{R}_2\text{NH}$ , *e.g.*,  $(\text{CH}_3)_2\text{NH}$  dimethyl amine,
- (3) a tertiary amine,  $\text{R}_3\text{N}$ , *e.g.*,  $(\text{CH}_3)_3\text{N}$  trimethyl amine.

The usual method of naming amines is illustrated by the above examples. In more complicated amines, the position of the group

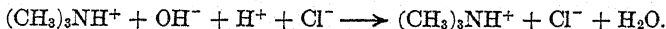
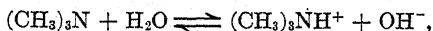
may be indicated and the name of the parent hydrocarbon given. Thus,  $(\text{CH}_3)_2\text{CHCHNH}_2\text{CH}_3$  is 2-amino-3-methylbutane. It should be noted that the group  $\text{NH}_2$  is called *amino* when present in an *amine* and *amido* when present in an *amide*.

**General Properties of Amines.** The simpler amines resemble ammonia. They are soluble in water and the solutions are basic. On boiling the solution the volatile amines are expelled. The boiling points of some of the simpler amines are given below.

BOILING POINTS OF SIMPLE AMINES

NAME	FORMULA	BOILING POINT	CLASS
Methyl amine	$\text{CH}_3\text{NH}_2$	- 7°	Primary amine
Dimethyl amine	$(\text{CH}_3)_2\text{NH}$	+ 7°	Secondary amine
Trimethyl amine	$(\text{CH}_3)_3\text{N}$	+ 4°	Tertiary amine
Ethyl amine	$\text{C}_2\text{H}_5\text{NH}_2$	+17°	Primary amine
n-Propyl amine	$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$	+49°	Primary amine

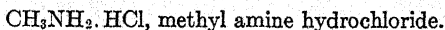
**Neutralization of Amines.** All three classes of amines are bases like ammonia. The water solutions turn red litmus blue and may be neutralized with acids. The salts which are thus formed are obtained as white solids by evaporating the solution. Like inorganic salts they are non-volatile solids, readily soluble in water and insoluble in organic solvents. Their water solutions are ionized. All these facts are best represented by the following ionic equations, using trimethylamine as the example:



Similar equations may be written for the primary and secondary amines. The chlorides may also be formed by bringing together the base and acid in an anhydrous medium:



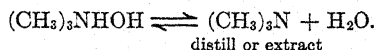
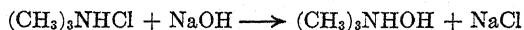
The salts of the amines are alkyl derivatives of the ammonium salts and are usually named on this basis, thus:  $\text{CH}_3\text{NH}_3\text{Cl}$ , methylammonium chloride;  $(\text{CH}_3)_2\text{NH}_2\text{Br}$ , dimethylammonium bromide;  $(\text{CH}_3)_3\text{NHNO}_3$ , trimethylammonium nitrate. The formulas of the salts are also written to show more clearly the original amine and are named as hydrochlorides, thus:



This method corresponds to an obsolete method of writing ammonium salts, thus:  $\text{NH}_3 \cdot \text{HCl}$ , the hydrochloride of ammonia.

Like ammonia, the amines form double salts with platinum chloride and gold chloride; for example,  $(\text{CH}_3\text{NH}_2)_2\text{PtCl}_6$  and  $\text{CH}_3\text{NH}_2\text{AuCl}_4$ . These salts are usually sparingly soluble in water, and are frequently used in isolating and identifying the amines. Their melting points are often characteristic, and a determination of the percentage of metal in the compound enables one to calculate the molecular weight of the amine.

**Preparation of Amines from Their Salts.** On treating a solution of the salt of an amine with sodium hydroxide, the free amine is formed in the solution. If the solution is then boiled, the amine will be expelled, if volatile; if the solution is extracted with ether, the amine will pass into the ether layer:



This behavior of the salts of the amines is exactly parallel to the reaction of ammonium salts. It shows that the amines like ammonia are *weak anhydro bases*. Thus, to obtain weak bases from their salts, we treat a solution of the salt with a strong base, and boil or extract; if the weak base is insoluble (as is the case with the higher amines), it will precipitate. This general method should be compared with the preparation of weak acids from their salts by the action of a strong non-volatile acid (p. 82).

**Basic Dissociation Constants.** The relative strength of weak bases may be best expressed in terms of a basic dissociation constant. This is similar to the acid dissociation constant which we have already mentioned (p. 83). All the weak organic bases belong to the class of substances which are called **anhydro bases**. A water solution of such a base contains the anhydro base itself (*e.g.*,  $\text{RNH}_2$ ), any undissociated hydrated base ( $\text{RNH}_3\text{OH}$ ) and the dissociated base ( $\text{RNH}_3^+ + \text{OH}^-$ ). In measuring the strength of an anhydro base we lump together both the unhydrated base,  $\text{RNH}_2$ , and the undissociated base,  $\text{RNH}_3\text{OH}$ , and call this total the free base. A measure of the strength of the base is thus the amount of dissociated base ( $\text{RNH}_3^+ + \text{OH}^-$ ) compared to the total free base ( $\text{RNH}_3\text{OH} + \text{RNH}_2$ ). Therefore, we write:

Basic Dissociation Constant ( $K_B$ )

$$= \text{Conc. OH}^- \times \left( \frac{\text{conc. of ion } (\text{RNH}_3^+)}{\text{conc. free base}} \right).$$

A solution containing equal molecular amounts of a weak anhydro base and its salt has a concentration of hydroxyl ion equal to the basic dissociation constant. The constant,  $K_B$ , for ammonia is

$2 \times 10^{-5}$  and the hydroxyl ion concentration of an ammonium hydroxide — ammonium chloride mixture is about  $10^{-5}$ ; since  $\text{conc. H}^+ \times \text{conc. OH}^- = 10^{-14}$ , the conc. of hydrogen ion in this solution is about  $10^{-9}$ .

The basic dissociation constants for some of the common amines are as follows:

Methyl amine,  $K_B = 5 \times 10^{-4}$ ,

Dimethyl amine,  $K_B = 5.4 \times 10^{-4}$ ,

Trimethyl amine,  $K_B = 5.9 \times 10^{-5}$ .

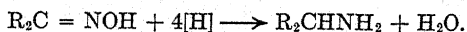
It is evident that they are somewhat stronger bases than ammonia itself. The relative strengths of certain bases are shown in the diagram in Fig. 20.

#### Preparation of Primary Amines.

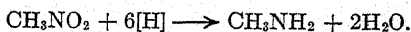
Special methods are employed for preparing a number of the different amines; we shall consider

only the general methods of preparing primary amines. These are as follows:

- (1) *Reduction of a Nitrile* (p. 155).
- (2) *Hofmann Reaction* (p. 151).
- (3) *Phthalimide Synthesis*. (This will be discussed when phthalimide is considered in Chap. XXIII.)
- (4) *Reduction of Oximes*:



- (5) *Reduction of Nitro Compounds*:



This last method is of little importance for the preparation of the type of amine we are here considering, but of great importance in

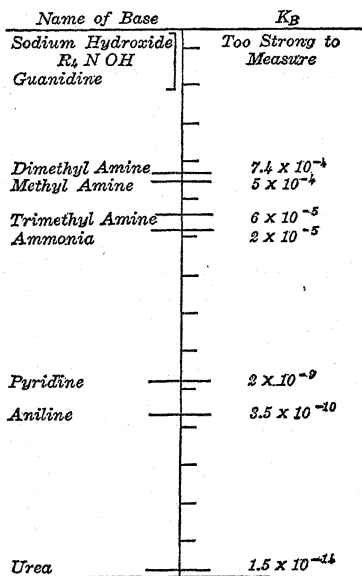
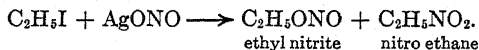


Fig. 20. The relative strengths of certain bases. The strongest bases are at the top; each unit of the scale corresponds to a ten-fold change in the basic dissociation constant.

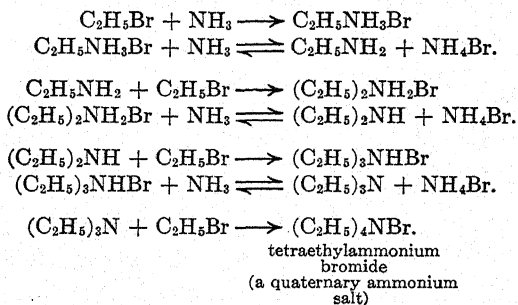
aromatic chemistry where the nitro compounds are easily obtained.

**Preparation of Nitro Compounds.** Compounds with the general formula  $C_nH_{2n+1}NO_2$  result from the action of alkyl halides on silver nitrite. At the same time some nitrite  $C_nH_{2n+1}ONO$  is also formed; the latter is an ester of nitrous acid (p. 30); the former is not.

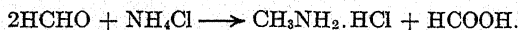


The nitro compounds can not be hydrolyzed to nitrous acid whereas such hydrolysis is the typical reaction of the nitrites. The fact that the nitro compounds are reduced to amines proves that the alkyl group is linked directly to the nitrogen atom. **Nitromethane**,  $CH_3NO_2$ , boils at  $101^\circ$ ; **nitroethane**,  $C_2H_5NO_2$ , at  $114^\circ$ ; the isomeric nitrites boil at  $-12^\circ$  and  $17^\circ$  respectively; the difference is striking.

**Preparation of Amines from Ammonia.** By heating ammonia with an alkyl halide, there is first formed the salt of a primary amine. This is because the alkyl halide combines with the ammonia. Unfortunately, the reaction does not stop here but forms secondary and tertiary amines and substances known as quaternary ammonium salts also. Methods have been devised for separating this unpromising mixture, and a number of amines have been prepared by this procedure, but generally it is unsatisfactory.



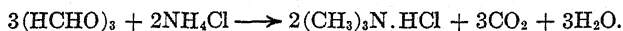
**Preparation of Methyl Amines from Formaldehyde.** By heating formaldehyde solution with a large excess of ammonium chloride, methylamine hydrochloride is formed:



The amine hydrochloride is separated from the excess ammonium chloride by

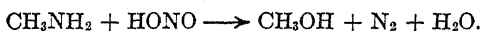
virtue of the fact that it is soluble in absolute alcohol while ammonium chloride is not.

When trioxymethylene (a solid) and solid ammonium chloride are mixed and heated together for some time, the mass liquefies and carbon dioxide is liberated. The product is largely trimethylamine hydrochloride:

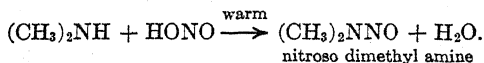


Since the initial materials are so cheap, monomethyl amine and trimethyl amine are readily prepared by these reactions.

**Reactions of Amines with Nitrous Acid.** Primary, secondary, and tertiary amines can be distinguished by their behavior towards nitrous acid. Primary amines react rapidly with an aqueous solution of nitrous acid, liberating nitrogen and forming the corresponding alcohol. The reaction may be illustrated with methylamine and nitrous acid:

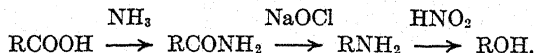


Secondary amines react slowly with nitrous acid forming **nitroso compounds** which often separate from the solution as an oil:

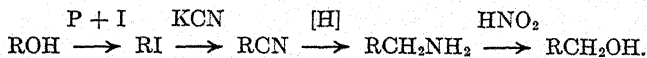


Tertiary amines form the corresponding salt (a tertiary amine nitrite) when treated with nitrous acid but undergo no further change; the amine may be recovered from the nitrite in the usual manner by adding alkali.

The reaction between a primary amine and nitrous acid provides a method of replacing the amino group by hydroxyl. Since the primary amine may be prepared from the corresponding amide, this presents an attractive scheme for converting the acid  $\text{RCOOH}$  into the alcohol  $\text{ROH}$ . This series of reactions is sometimes called "coming down the series."

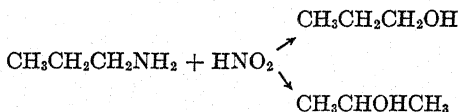


A somewhat similar series of reactions would seem to provide a method of "going up the series":



The difficulty with both these schemes lies in the fact that the reaction between nitrous acid and a primary amine often takes an abnormal course when there are more than two carbon atoms in the molecule. For example, *n*-propyl

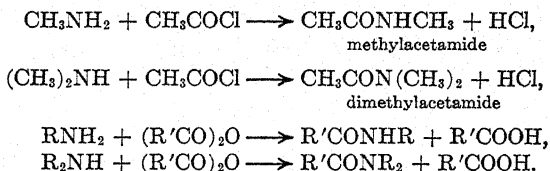
amine when treated with nitrous acid yields a mixture of *n*-propyl alcohol and isopropyl alcohol.



The formation of *isopropyl* alcohol is most unexpected and involves a **molecular rearrangement**. In certain cases the product may be entirely that resulting from a molecular rearrangement.

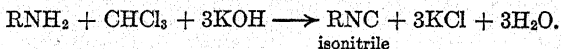
This abnormality of the reaction between nitrous acid and amines makes the use of this reaction very unreliable either in increasing or decreasing the number of carbon atoms in a chain.

**Acylation of Amines.** The primary and secondary amines (but *not* the tertiary) can be acylated by interaction with an acid chloride or an acid anhydride. The products are alkylated amides; on hydrolysis, the original amine is regenerated. The following equations illustrate these reactions:



**Tests for Amines and Amides.** Amides are distinguished from amines by their inability to form salts with acids (in water solution) and by the formation of ammonia on alkaline hydrolysis. The amines can not be hydrolyzed with either acids or bases. Both amides and *primary* amines liberate nitrogen when treated with nitrous acid but the products are different; the former yields an acid, the latter an alcohol.

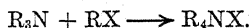
There are a number of tests to enable one to distinguish between a primary, a secondary, and a tertiary amine. The difference in behavior with nitrous acid is often used; if nitrogen is evolved a primary amine is present (it having been first proved that the compound is not an amide). Another characteristic reaction of primary amines is the peculiarly offensive odor produced when they are warmed with chloroform and potassium hydroxide. This is due to the formation of an isonitrile (p. 155).



Secondary and tertiary amines may be distinguished the one from the other by (a) the nitrous acid reaction mentioned above (p. 160) and (b) the fact that secondary amines but not tertiary amines may be acylated. A method of separating primary, secondary, and tertiary amines will be considered in a later chapter (p. 350).

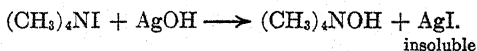
#### QUATERNARY AMMONIUM COMPOUNDS

We have seen that (p. 159) when a tertiary amine is heated with an alkyl halide the two combine, forming a substance known as a quaternary ammonium salt:



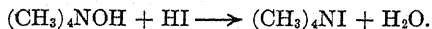
For example, trimethyl amine,  $(CH_3)_3N$ , when heated with methyl iodide yields tetramethylammonium iodide, a quaternary ammonium salt.

**Physical and Chemical Properties.** Quaternary ammonium salts resemble the salts of amines in their physical properties, being crystalline solids soluble in water. They differ very markedly, however, in their chemical behavior. The salts of the amines when treated with a strong base like sodium hydroxide are decomposed forming the free amine. The quaternary ammonium salts do not react with sodium hydroxide in aqueous solution. The reason for this becomes evident when one examines the product of the reaction of silver hydroxide on a quaternary ammonium iodide. In this case a reaction does take place because silver iodide is insoluble in water:



If the silver iodide is filtered off, the resulting aqueous solution is found to be *strongly alkaline*; on evaporation at low temperature a crystalline solid is obtained which has the composition corresponding to  $(CH_3)_4NOH \cdot 5H_2O$ . This substance (which is very deliquescent) is a strong base comparable with potassium or sodium hydroxide. It will absorb carbon dioxide from the air, forming a carbonate. An examination of the properties of the aqueous solution of this strong base shows that it is a solution of the hydroxyl ion and the quaternary ammonium ion,  $(CH_3)_4N^+$ . When neutralized with an acid, the quaternary ammonium base

forms the corresponding salt. In this way the iodide may be regenerated by neutralizing the solution with hydrogen iodide.



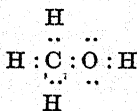
**Polar and Non-Polar Valences.** When we write the structure of tetramethylammonium iodide as  $(\text{CH}_3)_4\text{NI}$ , it is somewhat misleading, since one might be inclined to think that the iodine atom was attached to the nitrogen in much the same manner as the alkyl groups. As a matter of fact, the behavior of the salt in water solution and its properties as a solid have shown beyond doubt that the compound is really composed of the two ions  $(\text{CH}_3)_4\text{N}^+$  and  $\text{I}^-$ . This is the case not only in water solution but also in the crystalline solid. It will be recalled that modern research has shown that the same thing is true of all the salts of strong inorganic acids and bases; for example, sodium iodide is really  $\text{Na}^+$  and  $\text{I}^-$ .

It is convenient to distinguish between the forces which hold the methyl groups to the nitrogen in the quaternary ammonium ion and the electrical forces which unite together the ions of opposite charge in the solid. The former are called *non-polar valences*, the latter *polar valences*. A large portion of inorganic chemistry is concerned with salts, and hence with polar valences. Organic chemistry, on the contrary, deals primarily with the non-polar type of valence; it is such valence forces which hold the carbon, hydrogen, and oxygen atoms together in ethyl alcohol, for example. They are also involved in the union of all the atoms composing the complex ion  $(\text{CH}_3)_4\text{N}^+$ . Although there are transitional cases where it is difficult to be certain whether the valence in question is to be considered as polar or non-polar, the student will find it very useful to have clearly in mind the distinctions between these two types of valence.

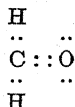
**The Electron Theory of Valence.** Modern physics has provided the chemist with a very satisfactory explanation of the distinctions between polar and non-polar compounds, and enabled him to correlate the occurrence of each class of compound with the kind of atoms which are present in the molecule. The essential facts involved in this development are usually presented in an elementary course in inorganic chemistry, and can be referred to but briefly here.

It will be recalled that the number of electrons outside the nucleus in a neutral atom correspond to the atomic number of the element, and that a certain number of these are in the inner shells. In the case of the elements of the first row of the periodic system, the inner shell contains two electrons; these are not available for the formation of chemical compounds. The electrons which are in the outer shell can be used in compound formation and are known as **valence electrons**. Their number is two less than the atomic number, in the case of elements in the first row of the periodic table. For carbon the number of valence electrons is 4, for nitrogen 5, for oxygen 6, and for fluorine 7. Similarly in the second row of the periodic table the number of outer electrons is 10 less than the atomic number. Thus the available electrons in sulfur are 6 and in chlorine 7. In general the halogen atoms have 7 valence electrons. Hydrogen has one electron, and this is available. In the formation of a polar compound the electron is *transferred* from the one atom to another; the atom which gives it up acquires a positive charge and the atom which accepts it becomes negatively charged. Electron transfer takes place in such a way as to complete a group of eight (octet) in one of the elements. *Polar valence is the result of a definite electronic transfer from one atom to another.* Thus, in sodium iodide we are really dealing with an aggregate of positive sodium ions and negative iodine ions.

The nature of non-polar valence is more obscure, and it is impossible to give the present physical conception of it without going very deeply into the subject of atomic physics. However, some useful pictures can be obtained by considering the subject qualitatively. Non-polar valence is the result of the *sharing* of two or more electrons between two atoms and this sharing results in a chemical union. The simplest example of this is the hydrogen molecule. If we represent the electrons by dots and a shared pair of electrons by : the hydrogen molecule will be written H : H. This same sharing of electrons is involved in nearly all the valence forces with which the organic chemist is concerned. Thus in electronic terms the structure of methyl alcohol is

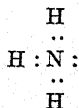


It is evident that the organic chemist uses a dash to represent a pair of shared electrons which would be represented in electronic terms by two dots. There is no advantage in most cases in writing electronic formulas for organic compounds since it would merely be the replacing of the valence bond by two dots. In the case of the double bonds between carbon atoms, four electrons seem to be held in common; the electronic formula for formaldehyde is:

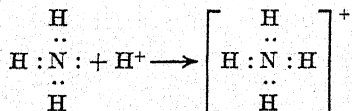


It will be noted that in these formulas the carbon and oxygen atoms all have a complete octet of electrons although this is accomplished by the economical process of sharing two electrons between two atoms.

**Electronic Formulas for Nitrogen Compounds.** In most compounds containing carbon, hydrogen, and oxygen, very little is to be gained by writing electronic formulas. When we turn to nitrogen, however, we meet with a different situation. The nitrogen atom has five valence electrons and the maximum number that can be in the outer shell is eight. In ammonia three of these are used in pairing with the electrons of three separate hydrogen atoms. This leaves in ammonia an *unshared pair of electrons*:

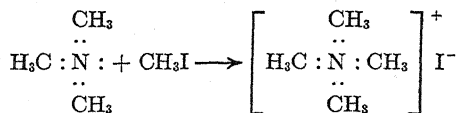


The basic properties of ammonia are due to this unshared pair which can attract and hold a hydrogen ion (often called a *proton*). The resulting product has a positive charge and is an ion because the total number of valence electrons is *one less* than the number belonging to each of the component atoms (8 as compared with  $3 + 1 + 5$ ). The essential reaction which is involved in the neutralization of ammonia by hydrochloric acid may be represented as follows:



In a similar way, in trimethyl amine three of the five electrons of the nitrogen atom are involved in forming pairs with three electrons from three different methyl groups. Here again an unshared pair of electrons is left on the nitrogen atom and, like ammonia, trimethyl amine is a base.

The unshared pair of electrons in trimethyl amine can not only combine with a proton, but it can also combine with another methyl group. This occurs slowly when the compound is heated with methyl iodide and the resulting product is the quaternary salt, tetramethylammonium iodide. All the nitrogen valence electrons are used in forming electron pairs. In this process the iodine atom has gained one electron, making a total of eight, and thus acquired a negative charge (since it has one more electron than in the neutral atom). The electron which the iodine atom has gained has been lost from the nitrogen, thus giving a positive charge of one unit to the whole ion:



It will be noted that of the eight electrons surrounding the nitrogen atom in the positive ion, four may be regarded as being contributed by the four carbon atoms and four from the nitrogen. This latter number is one less than the number of electrons associated with this normal nitrogen atom, and it is the loss of this electron which gives the positive charge to the ion.

We are now ready to consider the distinction between the tetramethylammonium ion  $(\text{CH}_3)_4\text{N}^+$  and the trimethylammonium ion  $(\text{CH}_3)_3\text{NH}^+$ . The latter is the substance which is formed by the addition of a proton to trimethyl amine when the amine is neutralized with an acid. The gain and loss of a proton from a nitrogen atom is a process which is instantaneous and reversible. Therefore, when we treat the trimethylammonium ion with a strong base, that is with a high concentration of hydroxyl ions, the hydroxyl ion takes away the proton forming water:

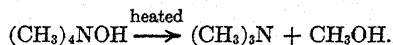


The same thing can not happen when the tetramethylammonium ion is treated with potassium hydroxide, because there is no

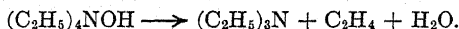
proton on the nitrogen. The pair of electrons holding the methyl group to the nitrogen does not break under these conditions. The fundamental reason for the different behavior of the proton and the methyl group is to be found by a physical study of atomic structure. For our purpose we must take it as a definite fact that the linkage of a proton to nitrogen is one which is rapidly formed or broken.

The water solution of tetramethylammonium hydroxide is nothing but an aggregate of hydroxyl ions and tetramethylammonium ions. Like potassium hydroxide, it has a high concentration of hydroxyl ions, and is therefore a strong base.

**Decomposition of Quaternary Bases on Heating.** Although the pair of electrons holding the methyl group to nitrogen is not broken in aqueous solution, it can be broken if the molecule is heated. Thus tetramethylammonium hydroxide decomposes on heating to give trimethyl amine and methyl alcohol. The hydroxyl ion combines with a methyl group and forms methyl alcohol:

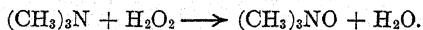


In the case of the quaternary ammonium bases which have higher alkyl groups the reaction proceeds somewhat differently. Here heating the compound usually results in the formation of a molecule of water, an unsaturated compound, and a tertiary amine:



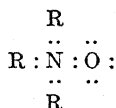
This decomposition of quaternary ammonium bases is sometimes useful in determining the structure of complex amines (p. 514), as it gives a method of eliminating the more complex group from the molecule in the form of an unsaturated hydrocarbon.

**The Amine Oxides.** When a tertiary amine is treated with hydrogen peroxide a very interesting substance known as an amine oxide is formed:



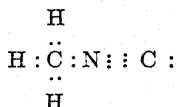
The amine oxides crystallize as hydrates, for example  $(\text{CH}_3)_3\text{NO} \cdot 2\text{H}_2\text{O}$  (m.p.  $98^\circ$ ). If we regard the nitrogen atom as having a valence of five, we would be inclined to write the structure of an amine oxide as  $(\text{CH}_3)_3\text{N} = \text{O}$ . The electronic formula equivalent to this would contain a nitrogen atom having ten electrons in the

outer shell,  $:\ddot{\text{N}}::\ddot{\text{O}}$ . All four electrons of a double bond are involved in the outer shell of each of the two connected atoms. Now a variety of considerations have convinced physicists that nitrogen can not have more than eight valence electrons in the outer shell. This excludes the formula of an amine oxide, which contains a double linkage; in place of this we must write the following:



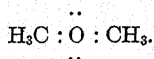
It will be noted that the nitrogen atom in this compound can be thought of as having one less electron than it normally carries, and the oxygen one more. There is thus internally an excess of electrons in one portion of the molecule and a deficiency in another. To emphasize this fact the formula is sometimes written as follows:  $(\text{CH}_3)_3\overset{+}{\text{N}} - \bar{\text{O}}$ . This is one case where the electronic formulas lead to a different result from formulas which would be written in terms of the simple valence theory.

**Structure of Isonitriles.** The isonitriles (p. 155) as methyl isocyanide,  $\text{CH}_3\text{NC}$ , are somewhat similar in their structure to the amine oxides. The electronic formula for methyl isocyanide is:

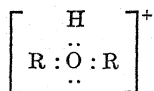


It will be noted that in this formula there are only three "bonds" joining the nitrogen and carbon (three pairs of electrons or a total of six), but that the nitrogen atom has *one less* electron than it usually carries and the carbon *one more*; therefore there is a difference in charge inside the molecule as in the case of the amine oxides. This may be represented by the + and - signs in the following formula:  $\text{R}\overset{+}{\text{N}} \equiv \bar{\text{C}}$ .

**Basic Properties of Oxygen and of Sulfur.** If we write the electronic formula of dimethyl ether it is evident that the oxygen atom contains two unshared pairs of electrons:



It might be expected that one or both of these pairs could add a proton just as the unshared pair in trimethyl amine adds a proton. We might thus predict that ethers would have basic properties. As a matter of fact, they do, but the tendency of the proton to stay attached to the oxygen is very much less than the tendency of the proton to stay attached to the nitrogen. The salts of an ether are therefore decomposed in water solution; if we treat an ether with concentrated hydrochloric acid, however, the ether dissolves in large quantities. A salt is formed of which the positive ion probably has the formula



The same thing is probably true of some other oxygen compounds. In certain cyclic compounds containing oxygen, the basic properties of oxygen are very pronounced, and in these cases the salts are stable in water solution. A consideration of these compounds will be postponed, however, until Chap. XXVIII.

Like oxygen, the normal sulfur atom contains six valence electrons, and the sulfur analog of an ether  $\text{R} : \ddot{\text{S}} : \text{R}$  might be expected to have basic properties. The attraction for a proton is very weak, however, and like the oxygen compound, the substances show no basic properties in aqueous solution.

**Amines and Quaternary Bases of Biochemical Interest.** Methyl amine, dimethyl amine and trimethyl amine are found in small quantities in nature. They are formed during bacterial decomposition of the proteins and other complex nitrogenous compounds. Trimethyl amine occurs in herring-brine and in the residues from the manufacture of beet-sugar.

Two **diamines** (*i.e.*, compounds with two amino groups) are formed in considerable quantities when proteins putrefy. They are **putrescine** (tetramethylene diamine),  $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$  (b.p.  $158^\circ$ ), and **cadaverine** (pentamethylene diamine),  $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$  (b.p.  $178^\circ$ ). They have a disagreeable odor and are poisonous. A tetramine, **spermine**, has been isolated from human sperm and its structure established as  $\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NH}(\text{CH}_2)_3\text{NH}_2$ . It will be noted that it may be regarded as putrescine with the group  $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2$  substituted on a nitrogen at each end of the chain.

**Choline.** A quaternary ammonium base,  $\beta$ -hydroxyethyltrimethyl-ammonium hydroxide,  $\text{CH}_2\text{OHCH}_2\text{N}(\text{CH}_3)_3\text{OH}$  occurs widely distributed in nature usually combined with an organic ester of phosphoric acid. Lecithin whose structure will be considered in the next chapter is an example of such a compound. In the body choline is set free from the lecithin of the foodstuffs and its presence seems to be essential to the proper utilization of fats by the animal body.

**Acetyl Choline,**  $\text{CH}_3\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{OH}$  is a substance with a very powerful physiological action (100,000 times more powerful than choline itself). When injected into the blood stream it causes a fall of the blood pressure. It has a powerful contractile effect on muscle tissue even in minute quantities. In certain cases, the animal body appears to utilize this action of acetyl choline in transmitting a nerve impulse to a muscle. Acetyl choline is liberated at the nerve endings when the nerve is stimulated.

### QUESTIONS AND PROBLEMS

1. Write structural formulas for: propionamide, dipropyl amine, dimethyl-ethyl amine, tetraethylammonium chloride, trimethylethylammonium iodide, isobutyramide, isopropyl amine.
2. Compare the physical and chemical properties of ammonia, methyl amine, and acetamide.
3. Outline a convenient process for separating pure trimethylammonium chloride from a mixture with sodium chloride and tetramethylammonium chloride.
4. How may primary amines be prepared from: (a) acids; (b) alcohols? Illustrate by outlining the steps in the synthesis of *n*-butyl amine from *n*-butyric acid and *n*-propyl alcohol.
5. Outline the steps in the synthesis of: (a) ethyl amine from methyl alcohol; (b) propyl amine from butyric acid.
6. Write equations showing several methods of preparing amides.
7. Trimethyl amine is heated with methyl iodide in an alcoholic solution. What product is formed? How does it differ from the compound which would result if dimethyl amine were used in place of the trimethyl amine?
8. Outline a convenient method of preparing: (a) methylammonium bromide (as pure as possible); (b) trimethyl amine; (c) isopropyl amine from acetone.
9. What products would you expect to obtain on heating: trimethylammonium hydroxide; dimethylpropylammonium hydroxide; a mixture of phosphorus pentoxide and propionamide; a solution of triethylammonium chloride in sodium hydroxide?

10. Explain clearly the following terms: polar valence, electron pair, valence electrons, non-polar valence.

11. By what methods would you distinguish between aqueous solutions of acetamide, methyl amine hydrochloride, trimethyl amine hydrochloride, tetramethylammonium chloride?

## CHAPTER IX

### POLYHYDRIC ALCOHOLS, FATS AND OILS

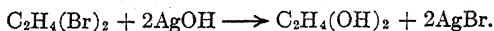
In previous chapters we have seen that many classes of organic compounds are characterized by having a certain reactive group in the molecule. Such reactive groups as the hydroxyl group of alcohols, the carboxyl group of acids, and the carbonyl group of aldehydes and ketones are known as **functional groups**. Up to this point we have considered only compounds which have one such functional group, but many complicated organic compounds contain several such groups and are known as poly-functional compounds. The study of such complex substances is simplified by the fact that usually each group reacts exactly as it would if it occurred alone. Thus the reactions of complicated substances may be predicted in many instances from a knowledge of simple compounds. Exceptions to this rule will be noted.

As an introduction to the study of poly-functional compounds we shall consider those substances which contain several hydroxyl groups in the molecule. These are known as the **polyhydric alcohols**. Two compounds of this class, ethylene glycol,  $\text{C}_2\text{H}_4(\text{OH})_2$ , and glycerine (glycerol),  $\text{C}_3\text{H}_5(\text{OH})_3$ , are of great importance; the first because of its cheap commercial production from ethylene, and the other because it is the alcohol which is combined with complex organic acids in animal fats and vegetable oils.

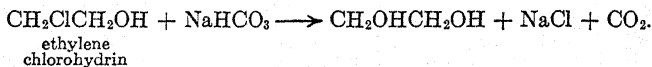
The simplest polyhydric alcohols are the **glycols**; these are compounds having the general formula  $\text{C}_n\text{H}_{2n}(\text{OH})_2$ . They are derivatives of the saturated hydrocarbons in which two hydrogens have been replaced by hydroxyl groups. Compounds containing two hydroxyl groups on the *same* carbon atom, *e.g.*,  $\text{RCH}(\text{OH})_2$ , are not included in this class. We have previously noted (p. 125) that attempts to prepare such a compound usually fail because of the elimination of water and the formation of an aldehyde or ketone. Therefore, the first member of the glycol series is ethylene glycol,  $\text{CH}_2\text{OHCH}_2\text{OH}$ , which has two hydroxyl groups on adjacent carbon atoms.

## GLYCOLS

**Preparation of Ethylene Glycol.** Just as an alcohol may be prepared from an alkyl halide, so a glycol may be prepared from the corresponding dihalide. Thus by the action of silver hydroxide on ethylene dibromide, ethylene glycol is formed:



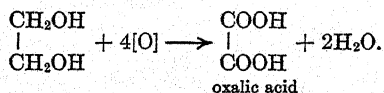
The industrial method of preparing ethylene glycol is to add hypochlorous acid to ethylene and to treat the resulting compound, ethylene chlorohydrin (p. 64), with a solution of sodium bicarbonate at 70°–80° for four to six hours. Under these conditions the chlorine atom is replaced by hydroxyl:



The direct transformation of ethylene to ethylene glycol has already been noted in connection with the action of potassium permanganate on ethylene; this method is of no preparative value.

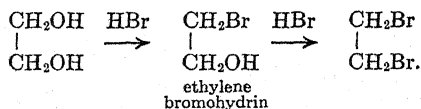
**Properties and Uses of Ethylene Glycol.** Ethylene glycol is a slightly sweet, mobile liquid, miscible with water in all proportions, but only slightly miscible with ether. It boils at 197° and solidifies at –11.5°. Ethylene glycol has been used extensively as a solvent and as a substance to be added to the water in the radiators of automobiles to prevent freezing under winter conditions. It is also used in the preparation of certain resins (p. 426).

**Chemical Properties of Ethylene Glycol.** The chemical reactions of ethylene glycol correspond to the fact that it has two primary hydroxyl groups. For example, it may be oxidized to the corresponding acid, oxalic acid, which contains two carboxyl groups:

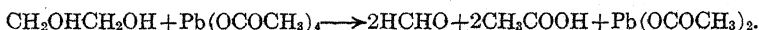


When treated with concentrated hydrochloric acid or hydrobromic acid, ethylene dichloride or dibromide is formed. By controlling the concentration of the acid and the temperature, the reaction

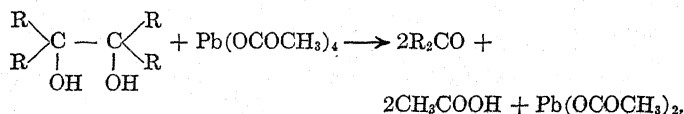
may be stopped at the first product, ethylene chlorohydrin or bromohydrin:



Ethylene glycol is dehydrogenated by lead tetraacetate, the C—C bond being ruptured to form two molecules of formaldehyde:



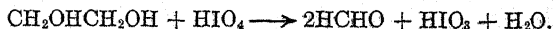
This reaction is general for all polyhydric alcohols in which two hydroxyl groups are on adjacent carbon atoms. Thus the general reaction may be formulated as:



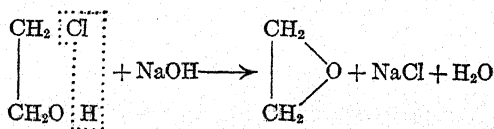
In this reaction the substituents represented by R's may be any alkyl group or hydrogen and they may all be the same or different. Lead tetraacetate may be prepared by warming a suspension of red lead  $\text{Pb}_3\text{O}_4$  in acetic acid and acetic anhydride:



This reaction is of particular value since it can be used to prepare a number of aldehydes and ketones hitherto obtained with difficulty. In place of lead tetraacetate, periodic acid may be employed with the same results:



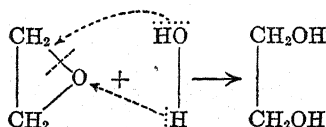
**Ethylene Oxide.** When ethylene chlorohydrin is heated with a solution of sodium hydroxide, hydrogen chloride splits out and a cyclic ether known as **ethylene oxide** is formed:



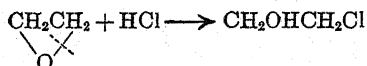
Ethylene oxide is soluble in water and boils at  $13^\circ$ . Mixed with

9 parts of carbon dioxide, it forms an important fumigant for foodstuffs and books because of the ease with which it can be removed by exposure to air.

Ethylene oxide, unlike diethyl ether, is very reactive. In most of its reactions the ether linkage is broken and a substituted ethyl alcohol derivative is formed. When heated with water in the presence of a small amount of acid as catalyst, ethylene glycol is formed:



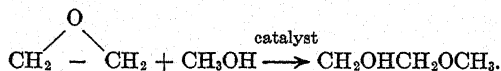
With hydrochloric acid it is changed into ethylene chlorohydrin:



The reaction between ethylene oxide and Grignard reagents has been considered previously (p. 144).

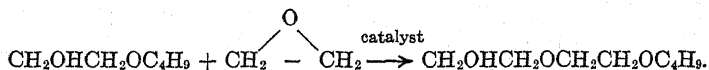
**Commercial Products from Ethylene.** We have pointed out previously that ethylene is the starting material for the synthesis of a large number of chemicals of industrial importance. At this time we shall consider a few of those products which are closely related to ethylene glycol. These compounds are generally made from ethylene oxide, which, as we have seen, is obtained from ethylene.

If ethylene oxide is treated with an alcohol in the presence of a small amount of a catalyst the two combine and a compound which is both an ether and an alcohol results:



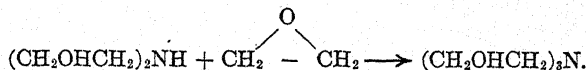
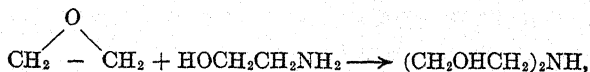
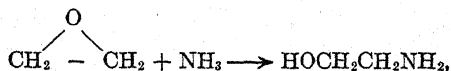
The monomethyl ether of ethylene glycol,  $\text{CH}_2\text{OHCH}_2\text{OCH}_3$ , the monoethyl ether,  $\text{CH}_2\text{OHCH}_2\text{OC}_2\text{H}_5$ , and similar compounds are readily prepared in this way. These substances are useful solvents because they are at one and the same time both alcohols and ethers, and for this reason readily dissolve a great variety of organic compounds. They are also miscible with water. This is

true even if the alcohol employed in their preparation is butyl alcohol. They are marketed under the name of *cellosolve*. Thus the monomethyl ether is *methyl cellosolve*, and the monobutyl ether,  $\text{CH}_2\text{OHCH}_2\text{OC}_4\text{H}_9$ , is called *butyl cellosolve*. The former boils at  $124^\circ$ , the latter at  $170.6^\circ$ . Closely related compounds are the ethers of diethylene glycol,  $\text{CH}_2\text{OHCH}_2\text{OCH}_2\text{CH}_2\text{OH}$ ; they are known as the *carbitols*. The carbitols are prepared by the action of ethylene oxide on the mono-ethers of ethylene glycol:



**Butyl carbitol**,  $\text{CH}_2\text{OHCH}_2\text{OCH}_2\text{CH}_2\text{OC}_4\text{H}_9$ , boiling at  $222^\circ$ , is particularly interesting as it is an excellent solvent and is completely miscible with water. It can be used for preparing homogeneous solutions containing both water and complex organic compounds insoluble in water.

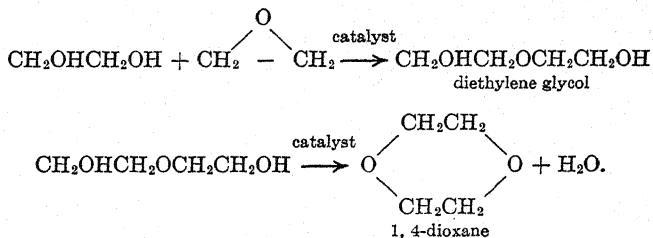
When ethylene oxide is treated with ammonia, a mixture of amino alcohols is formed according to the following equation:



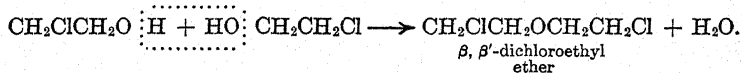
These compounds are marketed under the names of the "**ethanolamines**." The final product of the reaction is known as triethanolamine. They are high-boiling, colorless, viscous liquids, alkaline in reaction, hygroscopic and miscible with water in all proportions. Their base strength is comparable to that of the simple aliphatic amines. The ethanolamines are being widely used as emulsifying agents, in the preparation of soaps, and to some extent as solvents.

Still another solvent which may be prepared from ethylene and which is related to ethylene glycol is a compound known as **1, 4-dioxane**. It is a liquid boiling at  $102^\circ$  and is miscible with water. It can be prepared by the dehydration of diethylene

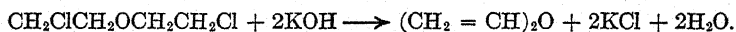
glycol, which in turn is prepared from glycol and ethylene oxide:



A solvent which has been mentioned in connection with petroleum refining is  $\beta$ ,  $\beta'$ -dichloroethyl ether. It is made from ethylene chlorohydrin by heating with concentrated sulfuric acid at  $90^\circ$ – $100^\circ$ :



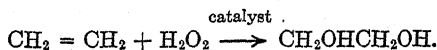
Divinyl ether,  $\text{CH}_2 = \text{CH} - \text{O} - \text{CH} = \text{CH}_2$  (b.p.  $28.3^\circ$ ), may be prepared from  $\beta$ ,  $\beta'$ -dichloroethyl ether by heating it with solid potassium hydroxide:



Divinyl ether is used as a general anesthetic, and in some respects it is claimed to be better than ether. It is interesting to note that this compound is related to ethylene and diethyl ether, both of which are widely used in anesthesia.

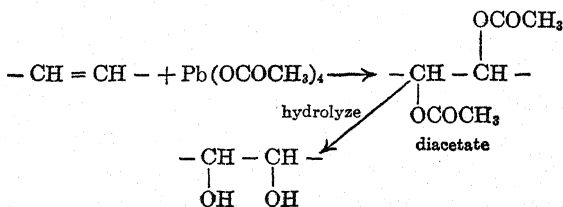
**Other Glycols.** Two other glycols are worthy of mention. **Propylene glycol**,  $\text{CH}_3\text{CHOHCH}_2\text{OH}$ , can be prepared from propylene by exactly the same reactions as are used in the preparation of ethylene glycol from ethylene. It resembles ethylene glycol in its physical properties but differs from it chemically in that it is a *secondary* as well as a *primary* alcohol. **Trimethylene glycol**,  $\text{CH}_2\text{OHCH}_2\text{CH}_2\text{OH}$ , is a by-product of the preparation of glycerol from fats. It is a viscous liquid boiling at  $214^\circ$  and miscible with water in all proportions. The corresponding dibromide may be prepared from it by the action of hydrobromic acid. This dibromide is known as **trimethylene dibromide**,  $\text{CH}_2\text{BrCH}_2\text{CH}_2\text{Br}$ ; we shall have occasion to refer to it again in connection with the synthesis of certain compounds.

**General Methods of Preparing Glycols.** The general methods of preparing glycols depend on the relative position of the hydroxyl groups. When the two groups are on adjacent carbon atoms, there are other methods which can be employed besides the ones outlined above. In general, the corresponding olefin is the starting material. For example, hydrogen peroxide and a catalyst, such as osmium tetroxide, will oxidize ethylene and its derivatives to 1, 2-glycols:

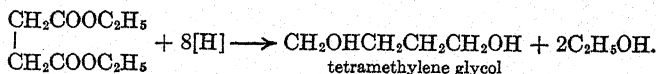


This reaction is carried out best in tertiary butyl alcohol as the solvent. It is somewhat analogous to the oxidation of olefins to glycols by potassium permanganate (p. 66).

In the case of a number of relatively complex compounds containing the ethylene linkage it has been found possible to prepare the glycols readily by the use of lead tetraacetate. The steps are as follows:



When the two hydroxyl groups are on the extreme ends of the carbon chain, the glycol can be formed from the ethyl ester of the corresponding acid with two carboxyl groups by reduction with sodium and alcohol or by catalytic hydrogenation. This is merely an application of a general method of preparing primary alcohols from esters (p. 100); it is illustrated below in the preparation of tetramethylene glycol:



Since acids of the general formula  $(\text{CH}_2)_n(\text{COOH})_2$  are readily available (Chap. X), the corresponding glycols,  $\text{CH}_2\text{OH}(\text{CH}_2)_n\text{CH}_2\text{OH}$ , can be easily prepared. The physical properties of some of the members of such a series of glycols are given in the table:

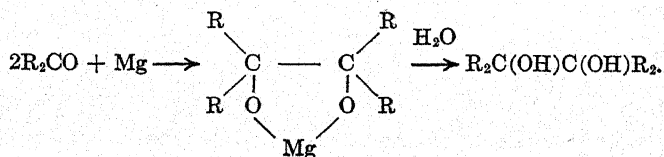
PHYSICAL PROPERTIES OF GLYCOLS,  $\text{CH}_2\text{OH}(\text{CH}_2)_n\text{CH}_2\text{OH}$ 

NAME	FORMULA	BOILING POINT	MELTING POINT	DENSITY
Ethylene glycol	$\text{CH}_2\text{OHCH}_2\text{OH}$	197.4°	-11.5°	1.1097(25°)
Trimethylene glycol	$\text{CH}_2\text{OHCH}_2\text{CH}_2\text{OH}$	214°	—	1.0526(18°)
Tetramethylene glycol	$\text{CH}_2\text{OH}(\text{CH}_2)_2\text{CH}_2\text{OH}$	230°	16°	1.020(20°)
Pentamethylene glycol	$\text{CH}_2\text{OH}(\text{CH}_2)_3\text{CH}_2\text{OH}$	239°	—	.994(18°)
Hexamethylene glycol	$\text{CH}_2\text{OH}(\text{CH}_2)_4\text{CH}_2\text{OH}$	250°	42°	
Heptamethylene glycol	$\text{CH}_2\text{OH}(\text{CH}_2)_5\text{CH}_2\text{OH}$	262°	22.5°	

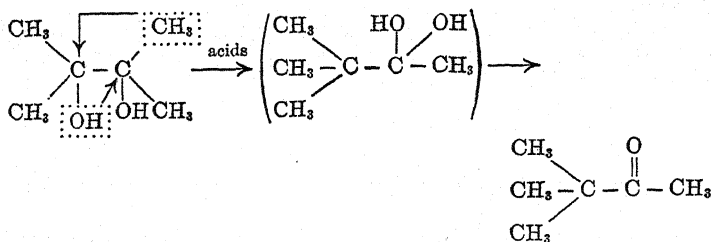
The first four members are all miscible with water and alcohol. The solubility in water decreases as the molecular weight increases.

**Nomenclature.** The names which are commonly assigned to the compounds we have been discussing are either trivial names which originated from the method of preparation or trade names which have been recently established. Glycols which belong to the series given in the table are named as indicated but this method applies only to this special group of glycols. By the Geneva system the glycols are named from the corresponding saturated hydrocarbons, adding to the end of the word the suffix "diol" and indicating by numbers the position of the groups. Thus propylene glycol is propanediol-1, 2; trimethylene glycol is propanediol-1, 3. The nomenclature of the corresponding halogen compounds has already been considered (p. 135).

**Pinacols.** The glycols which have two adjacent hydroxyl groups and four alkyl groups symmetrically arranged can be prepared by the reduction of ketones in alkaline medium (p. 116). The simplest of these is pinacol,  $(\text{CH}_3)_2\text{COHCOH}(\text{CH}_3)_2$ , which is prepared from acetone. It is a liquid boiling at 172°; it forms a white, crystalline hydrate when treated with water. Similar compounds can be prepared by the reduction of other ketones with metallic magnesium:

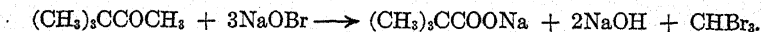


**Pinacol Rearrangement.** The pinacols are of interest because of a remarkable reaction which they undergo when heated with acids. A molecule of water is eliminated and a *rearrangement of the alkyl groups* takes place with the formation of a ketone:



Such a reaction is called a *molecular rearrangement*; another example of a rearrangement was considered in the previous chapter in connection with the action of nitrous acid on primary amines (p. 161). The intermediate shown above is probably the first product of the shift of groups. In spite of a great deal of study, we are still very much in the dark as to the mechanism by which such a shift can take place. Fortunately, it is a rather rare occurrence.

The most convenient way of preparing certain ketones is the rearrangement of a pinacol. The compound formed from pinacol itself is called **pinacolone**. It is a liquid boiling at 106°. The proof that such a rearrangement has really taken place when pinacol is dehydrated is furnished by the fact that the ketone on treating with sodium hypobromite yields bromoform and trimethyl acetic acid:



The structure of the latter can be definitely established by several methods. It is thus clear that a shift of methyl groups has taken place in the transformation of pinacol to pinacolone.

### GLYCEROL

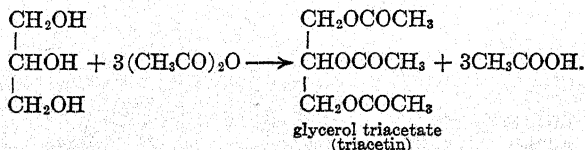
Glycerol or, as it is often called, glycerine, is a trihydroxy derivative of propane having the formula  $\text{CH}_2\text{OHCH}_2\text{OHCH}_2\text{OH}$ . It is formed whenever an animal fat or a vegetable oil is boiled with sodium hydroxide. If we take a typical animal fat, such as tallow from the beef animal, and boil it with sodium hydroxide, it

changes into a thick mass which with sufficient water will form a clear solution. On adding sulfuric acid to this solution we obtain a precipitate which consists of a mixture of two acids of the fatty acid series, namely, palmitic acid,  $C_{15}H_{31}COOH$ , and stearic acid,  $C_{17}H_{35}COOH$ . Since these acids are insoluble in water, they separate when the solution of their sodium salts is made acid. If we evaporate the water solution, we shall find that after distilling off all the water a viscous high-boiling liquid remains together with sodium sulfate. This liquid is **glycerol**. It can be purified by distillation under diminished pressure.

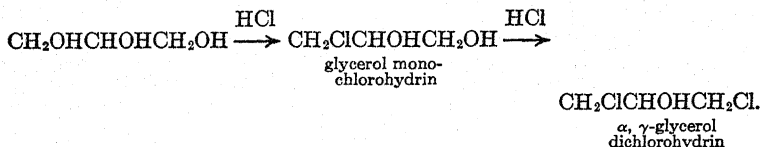
The industrial preparation of glycerol is essentially that just outlined. It is thus a by-product of the manufacture of the fatty acids or their salts — the soaps. It has also been manufactured by the fermentation of sugar by yeast under special conditions. The mixture is kept somewhat alkaline and sodium bisulfite is added during the fermentation. During the World War very large quantities of glycerol were prepared in this way in Germany. It has been sold as an anti-freeze for automobile radiators. It is used in the manufacture of cosmetics, dentifrices, and in the preparation of inks and mucilages.

**Physical and Chemical Properties.** Glycerol is a viscous, non-toxic, colorless liquid with a sweetish taste. It is miscible in all proportions with water. When pure it can be made to solidify by cooling and the crystals melt at  $17^{\circ}$ ; the liquid is very prone to "supercooling" and it is often extremely difficult to start the crystallization. The usual samples of glycerol contain varying proportions of water since glycerol is hygroscopic. It boils at  $290^{\circ}$ . If kept long at its boiling point, it undergoes partial decomposition, and is therefore best purified by distillation under diminished pressure.

Glycerol contains two primary hydroxyl groups and one secondary group. The presence of three hydroxyl groups in the molecule is established by the fact that when acylated, three acyl groups are introduced into the molecule. As an example of this the preparation of the triacetate may be given:



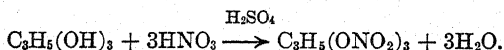
When treated with gaseous hydrochloric acid one or both of the primary hydroxyl groups are replaced by chlorine. The products are called glycerol chlorohydrins:



The structure of the final product is established by the fact that on oxidation it yields a *ketone*, dichloroacetone,  $\text{CH}_2\text{ClCOCH}_2\text{Cl}$ .

**Nitroglycerine and Dynamite.** The trinitrate of glycerol is called nitroglycerine. It has the formula  $\text{CH}_2(\text{ONO}_2)\text{CH}(\text{ONO}_2)-\text{CH}_2(\text{ONO}_2)$ . It is an oily liquid which solidifies at  $12^\circ$ . It is a powerful explosive which is very sensitive to shock and dangerous to transport. Nobel<sup>1</sup> discovered in 1867 that if nitroglycerine was absorbed by some inert porous material such as kieselguhr (silica), a powerful but relatively safe explosive was formed. This was *dynamite*. Dynamite today is commonly manufactured by using wood pulp or sawdust as the solid absorbent materials and adding solid ammonium nitrate.

Nitroglycerine is prepared by the action of concentrated nitric and sulfuric acids on glycerol. The temperature must be carefully controlled:



## FATS AND OILS

Having now considered the chemistry of glycerol, we are in a position to attack the complicated subject of the fats and oils. First of all, a word of warning is necessary about the use of the term oil. It is a much abused expression and originally probably connoted merely a somewhat viscous liquid; for example, sulfuric acid was called "oil of vitriol." The organic substances which are commonly called oils can be divided into three classes: (1) the **mineral oils**, which are petroleum products; (2) **essential oils**, which are fragrant, volatile constituents of plants and plant products (*e.g.*, oil of wintergreen, oil of cinnamon, oil of cloves); (3)

<sup>1</sup> A. B. Nobel (1833-1896). A Swedish chemist and pioneer in the field of explosives. He dedicated his fortune to the establishment of the Nobel prizes.

the vegetable oils, which are esters of glycerol. These vegetable oils together with the animal fats form a distinct class which we are now to consider. Generally speaking, if a member of this class is liquid at room temperature, it is called an oil and if solid, a fat. Coconut oil and palm oil are liquids at temperatures which prevail in the tropics where they are obtained but they are solids at usual room temperature in the temperate zone.

**The Acids Obtained from Fats and Oils.** When tallow is hydrolyzed by the action of sodium hydroxide, a mixture of stearic and palmitic acids is obtained. This would indicate either that the two acids were combined with one molecule of glycerol or that the natural fat was a mixture of two compounds. Other evidence obtained by the examination of tallow seems to show that it is a mixture of the tripalmitic ester of glycerol (called **tripalmitin**) and the tristearic ester (called **tristearin**).

If we examine in a similar way other animal fats and oils, we always find glycerol and a mixture of acids as the products of saponification. The more important of these acids are listed below in the table, together with their physical properties.

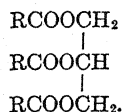
THE ACIDS WHICH OCCUR COMMONLY IN FATS AND OILS

NAME	FORMULA	STRUCTURE	MELTING POINT
Palmitic acid	$C_{16}H_{31}COOH$	$CH_3(CH_2)_{14}COOH$	$63^\circ$
Stearic acid	$C_{17}H_{33}COOH$	$CH_3(CH_2)_{16}COOH$	$69^\circ$
Oleic acid	$C_{17}H_{33}COOH$	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	$14^\circ$
Linoleic acid	$C_{17}H_{31}COOH$	Has two double bonds	liquid at $0^\circ$
Linolenic acid	$C_{17}H_{29}COOH$	Has three double bonds	liquid at $0^\circ$

It will be noted that the last three are unsaturated acids which are related to stearic acid in so far as they contain the same carbon skeleton (seventeen carbon atoms and a carboxyl group). Each belongs to a separate homologous series with a different general formula. Palmitic and stearic acids which belong to the fatty acid series have the general formula  $C_nH_{2n+1}COOH$ ; oleic acid

has the formula  $C_nH_{2n-1}COOH$ , linoleic  $C_nH_{2n-3}COOH$ , and linolenic  $C_nH_{2n-5}COOH$ .

**Glycerides.** The esters of an acid with glycerol are called glycerides and are named as follows: **triacetin** is the tri-acetic ester of glycerol; **tripalmitin** is the tri-palmitic ester of glycerol; **triolein** is the tri-oleic ester of glycerol. The general formula is:



The melting points of some common glycerides are given below:

	m.p.
Tripalmitin.....	60°
Tristearin.....	71°
Triolein.....	17°
Trilinolein.....	oil below 0°.

It will be noticed that the glycerides of the saturated acids, like the free acids themselves, melt at a much higher temperature than the glycerides of the unsaturated acids. Thus, the relatively low melting point of a vegetable oil, in comparison to that of an animal fat, is due to the fact that the former contains unsaturated glycerides. The essential difference between tallow and cottonseed oil is the absence of a few hydrogen atoms in the latter.

APPROXIMATE COMPOSITION OF SOME FATS AND OILS

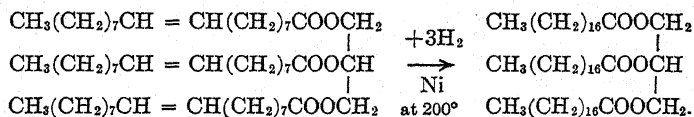
NAME	TRISTEARIN AND TRIPALMITIN	TRIOLEIN	TRILINOLEIN	OTHER GLYCERIDES
	Per cent	Per cent	Per cent	Per cent
Tallow	75	25	0	0
Butter Fat	53	39	0	8
(There is considerable tributyrin in this fat)				
Olive Oil	25	70	5	0
Cottonseed Oil	25	25	47	3
Linseed Oil*	8	18	30	44
Soy Bean Oil	7	33	52	8
Tung Oil**	5	13		82

\* Contains about 30 per cent of the glycerides of linolenic acid.

\*\* Contains about 73 per cent of eleostearic acid,  $C_{17}H_{33}COOH$ , which is isomeric with linolenic acid.

**Fats as Foods.** Together with the carbohydrates (Chap. XVII) and proteins (Chap. XXXI) fats constitute the important source of energy for the animal body. In the process of digestion the fats are hydrolyzed and eventually burned to carbon dioxide and water. The steps in this process are not known. It was at one time thought that the animal could dehydrogenate fatty acids, but it has been shown that if a young animal be fed on a diet entirely free from unsaturated acids, the animal suffers from a so-called fat deficiency disease. This would indicate that such acids as oleic and linoleic cannot be formed from stearic by the animal organism. If this be so, then the unsaturation of animal fats must be eventually traced to vegetable fats and oils. These, we have seen, are often highly unsaturated. The green plant is able to synthesize both saturated and unsaturated acids. It is interesting that only acids with an even number of carbon atoms are found in plants and animals.

**Hydrogenation of Vegetable Oils.** A large industry exists which transforms vegetable oils into solid fats. The chemistry of this process is extremely simple. It is based on the reaction known as *catalytic hydrogenation* which we have already considered (p. 66). The following reaction illustrates the transformation of triolein to tristearin:



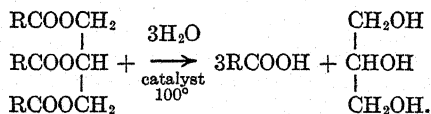
The hydrogenation of vegetable oils is controlled in order to yield the type of product desired. Thus, if a synthetic lard is wanted for cooking purposes, the reduction is stopped when partially complete; otherwise a material comparable to tallow is obtained. The term "hardening" is sometimes given to this process of hydrogenating a vegetable oil.

**Butter.** Butter differs from the other fats in containing a small amount of tributyrin, the glyceride of butyric acid. When butter has stood for some time it slowly becomes rancid because of the liberation of free butyric acid by the hydrolysis of the glyceride. Although only a very small per cent of the glyceride may be decomposed, the butter is quite unfit for use because of the disagreeable smell of butyric acid. The butyric acid may be removed by washing the butter with an aqueous solution of sodium bicarbonate, or by blowing steam through the molten butter which volatilizes the butyric acid. Butter thus freed from butyric acid is called *renovated butter*. In order to restore to it some of the characteristic flavor and consistency of natural butter, it is usually churned with skim milk under such conditions that it separates in more or less of a conglomerate containing considerable amounts of water.

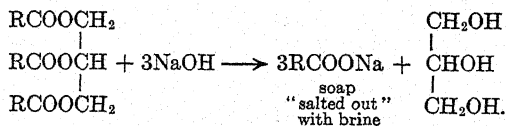
**Oleomargarine** and various vegetable butters and other butter substitutes are mixtures of vegetable oil and animal fats or partially hydrogenated vegetable oils of such consistency as to resemble butter. To simulate the mechanical structure of butter and its characteristic flavor such substances are often agitated with milk before being put on the market. They must be artificially colored. In many states, to prevent fraud, there are special laws covering the sale of oleomargarine and other special butters.

**Candle Stock.** A mixture of palmitic and stearic acids is prepared industrially and sold under the name of **stearin**. It is a waxlike solid, used for the manufacture of candles and sometimes called candle stock. For the preparation of this substance animal fats or hydrogenated oil must obviously be used, since only the high-melting acids obtained from saturated glycerides yield a solid material suitable for candles.

**Hydrolysis of Fats.** The hydrolysis of fats to produce the free acids is brought about by heating them with a catalyst and water. The catalyst used is usually either a small amount of lime or a complex organic acid known as **Twitchell's reagent**. The reaction goes to completion, probably because the acids are insoluble and separate from the mixture. The solution from which the insoluble acids have been separated is distilled and glycerol is obtained:



**Manufacture of Soap.** Soap is prepared by boiling animal fats and vegetable oils with sodium hydroxide. When the reaction is complete, salt is added which causes the complete separation of the sodium salts of the fatty acids: these are lighter than water, float on the surface, and are removed. The glycerol in the residual brine may be obtained by distillation:



The soaps which come on the market are the sodium salts of the fatty acids mixed with a number of other materials which give them odor, color, and cleansing properties. The hydrogenated

vegetable oils are much used in soap manufacture. A satisfactory soap can not be made from an oil like cottonseed oil itself but after hydrogenation the oil is the equivalent of tallow.

**Rosin** is also used in the manufacture of soaps. It is the amorphous yellow residue left after the distillation of *spirits of turpentine* from the sap of coniferous trees. It is an organic acid (or acid anhydride) of high molecular weight (p. 505) and, therefore, reacts with bases to form salts. Solutions of sodium "rosinate" have cleansing power and produce lather like soap solutions. Many cheap laundry soaps contain much rosin. Shaving soap usually contains some rosin to produce good lather; it also contains glycerol and gum to prevent too rapid drying.

**Cleansing Action of Soap.** Why is a solution of sodium stearate (soap) a cleansing agent, while sodium acetate is not? The explanation is connected with the large molecular weight of palmitic and stearic acids. In water solution, the large organic ions form a complex which is so large as to have colloidal properties. Thus, a solution of sodium palmitate or sodium stearate differs from one of sodium acetate by being **colloidal**. Colloidal solutions have the property of causing other substances to pass into colloidal solution or to form emulsions; it is for this reason that a solution of soap emulsifies oil, grease, and dirt and thus removes them.

**Sulfonated Soaps.** Another group of soaps recently introduced are the sulfonic acid salts of long chain aliphatic alcohols, which have the general formula  $\text{CH}_3(\text{CH}_2)_n\text{OSO}_3\text{Na}$  where  $n$  is ten or more. They are marketed either as solids or in solution. Lauryl alcohol,  $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OH}$ , cetyl alcohol,  $\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OH}$ , and stearyl alcohol,  $\text{CH}_3(\text{CH}_2)_{16}\text{CH}_2\text{OH}$  are used to make these new detergents. These alcohols are made today by catalytic hydrogenation of the esters of the corresponding acids (p. 100). Generally, the glycerides themselves are reduced; tripalmitin under these conditions yields cetyl alcohol and glycerol.

The advantage of these soaps over those from the fatty acids is that they may be used in slightly acid solutions (which would precipitate fatty acids from ordinary soaps) and in salt and hard waters since their calcium and magnesium salts are soluble.

## DRYING OILS

**Drying of Oil Paints Is Oxidation.** Linseed oil and certain other vegetable oils, such as tung and soy bean oil, have the peculiar property of slowly absorbing oxygen from the air and chang-

ing into a hard transparent solid. This property is particularly manifested if a thin layer of the oil is spread on some surface such as wood which is exposed to the air. This oxidation of linseed oil is commonly and quite erroneously called *drying*. It is the basic chemical reaction in the so-called drying of oil paints.

The linseed oil as it comes from the flax seed (called **raw linseed oil**) absorbs oxygen very slowly; paint made from it would be too slow drying for most purposes. It has been found that by heating linseed oil to 200° in the presence of certain inorganic substances it undergoes some chemical change, with the result that it will now absorb oxygen much more rapidly at room temperature. Oil which has been thus treated is called **boiled linseed oil** and is the material used in the manufacture of practically all oil paints.

Our knowledge of the chemistry of the drying of linseed oil is very meager. The ability of an oil to combine with oxygen seems to be connected with the presence of glycerides of highly unsaturated acids such as linolenic acid. We always find a high percentage of such glycerides in oils which have drying properties. It is probable that the oxygen of the air combines with the unsaturated linkages and that a polymerization somewhat analogous to the polymerization of isoprene then takes place. If this is true, dried paint is a polymerized, oxidized glyceride of linolenic acid.

**Oil Paints.** Oil paints are merely a suspension of very finely divided pigments in linseed oil. The pigments are for the most part inorganic compounds such as basic lead carbonate (white lead), lead oxide (red lead), etc. When an especially quick-drying oil paint is desired the oil is sometimes diluted with spirits of turpentine which really dries in the sense that it evaporates and leaves a thin coating of the material behind; this then "dries" by absorbing oxygen in the usual manner. Certain substances called **driers** are sometimes added to the paint. They act catalytically to accelerate the oxidation process.

Oilcloth is made by covering cloth with boiled linseed oil and letting it dry. Linoleum is a "dried" mixture of linseed oil and cork which have been pressed together. Tung oil is also used for the same purpose.

In connection with the general chemistry of paints one should bear in mind that there is a great distinction between oil paints, which we have just been discussing, and various other forms of paint or paint-like substances, such as shellac, varnishes, and lacquers. These substances are solutions of organic materials in volatile solvents, and their drying is due to the evaporation of the solvent, the organic material being left behind as a thin coating. For many purposes lacquers of various sorts are now replacing oil paints. Automobiles, for example, and many other metal surfaces are painted with a lacquer prepared from cellulose.

**Analysis of Fats and Oils.** Certain convenient methods of analysis are frequently employed in studying fats and oils. By saponifying a weighed sample of the material with potassium hydroxide, the **saponification number** may be obtained. It is defined as the number of milligrams of potassium hydroxide required to saponify one gram of fat.

The degree of unsaturation of a fat or oil can be determined by allowing a known weight of the material to react with iodine in a solution of mercuric chloride in alcohol. The amount of halogen which combines with the double linkages of the various unsaturated glycerides can be readily determined. It should be noted carefully, however, that the direct combination of iodine with double linkages is very slow and only proceeds in this instance at a convenient rate because of the special reagent employed. The results are expressed in terms of what is known as the **iodine number**, *which is the number of grams of iodine combining with 100 g. of fat*. This number is obviously greater the more unsaturated glycerides are present. Typical iodine numbers are given in the tables below.

IODINE NUMBER OF FATTY ACIDS AND THEIR GLYCERIDES

	FREE ACID	GLYCERIDE
Oleic	90.0	86.2
Linoleic	181.4	173.5
Linolenic	274.1	262.1

IODINE NUMBER OF CERTAIN FATS AND OILS

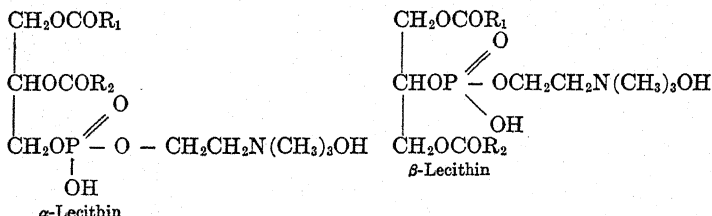
Tallow	35-40	Cottonseed Oil	104-116
Lard	48-64	Soy Bean Oil	135-150
Olive Oil	77-91	Tung Oil	150-170
		Linseed Oil	175-201

**Reichert-Meisss Number.** Butter contains a relatively large amount of the glycerides of the lower fatty acids; artificial butters and renovated butters contain much less. It is, therefore, important to have a method of determining the percentage of the glycerides of the lower fatty acids in a sample of butter or other fat. This is done by saponifying 5.5 grams of the fat, acidifying with sulfuric acid and distilling the aqueous solution until a definite volume of distillate is collected. The lower fatty acids are volatile with steam and are

largely in the distillate. The number of cubic centimeters of 0.1 *N* potassium hydroxide required just to neutralize this distillate is the Reichert-Meissl number of the fat.

**Phosphatides.** A group of glycerides closely related to the fats and oils is known as the phosphatides. They occur widely distributed in animal and plant cells but usually in small amounts. They may be regarded as fats in which one acyl group has been replaced by a complex phosphoric acid. Like the fats, they usually are present in nature as a mixture of several compounds containing different closely related acyl groups (*e.g.*, stearyl and palmityl). For this reason probably no representative of the phosphatides has been obtained in a pure state.

The **lecithins** ( $\alpha$  and  $\beta$ ) are the commonest phosphatides. Their structures are usually represented by the following formulas, where  $R_1CO$  and  $R_2CO$  represent the acyl groups of the higher fatty acids:



On hydrolysis the lecithins yield glycerol, a mixture of fatty acids, phosphoric acid, and the quaternary base, choline,  $\text{CH}_2\text{OHCH}_2\text{-(CH}_3)_3\text{NOH}$  (p. 170). Large amounts of the lecithins are found in egg yolk, liver, and brain. Like the fats they are soluble in ether and many other organic solvents but insoluble in water.

**Waxes.** A group of plant and animal products having somewhat the same physical properties and solubilities as the fats are the **waxes**. They are entirely different, however, in their chemical composition and reactions. Waxes are usually a mixture of higher alcohols of the methyl alcohol series ( $\text{C}_n\text{H}_{2n+1}\text{OH}$ ) with esters of these same alcohols and the fatty acids; in some waxes, certain amounts of higher hydrocarbons are also present. Waxes may be distinguished from the fats by the fact that when boiled with sodium hydroxide they are not transformed into water-soluble products. (The higher alcohols are, of course, insoluble in water and aqueous sodium hydroxide.) Together with sterols

(Chap. XXVII) they are the "unsaponifiable portion" left when a chloroform or ether extract of plant or animal tissue is hydrolyzed with alkali. (The esters of the higher alcohols present in the waxes are converted to the higher alcohols themselves by this treatment, of course.)

The alcohols,  $C_{30}H_{61}OH$ , **myricyl alcohol**, and  $C_{26}H_{53}OH$ , **ceryl alcohol**, are frequently found in waxes. **Beeswax** is largely myricyl palmitate,  $C_{15}H_{31}COOC_{30}H_{61}$ . It is widely used in the manufacture of polishes and in pharmaceutical preparations. **Chinese insect wax** is obtained from a deposit made by a parasitical insect on certain trees in Asia. It is largely ceryl cerotate,  $C_{25}H_{51}COOC_{26}H_{53}$ . (Cerotic acid is  $C_{26}H_{51}COOH$ .) **Carnauba wax** has an exceptionally high melting point ( $83^{\circ}$  to  $86^{\circ}$ ). It is extracted from the leaves of a certain Brazilian palm. It is largely  $C_{25}H_{51}COOC_{30}H_{61}$ .

**Higher Polyhydric Alcohols.** Alcohols having four, five, and six hydroxyl groups are known. Many of these are found in nature. **Erythritol**,  $CH_2OH(CHOH)_2CH_2OH$ , occurs, usually as an ester, in many lichens and fungi. The tetranitrate of erythritol is used in medicine for certain cardiac disturbances. **Arabitol**, **xylitol**, and **adonitol** are pentahydric alcohols. They all may be represented by the formula  $CH_2OH(CHOH)_3CH_2OH$ . The hexahydric alcohols, **mannitol**, **dulcitol**, and **sorbitol**,  $CH_2OH(CHOH)_4CH_2OH$ , also occur in nature.

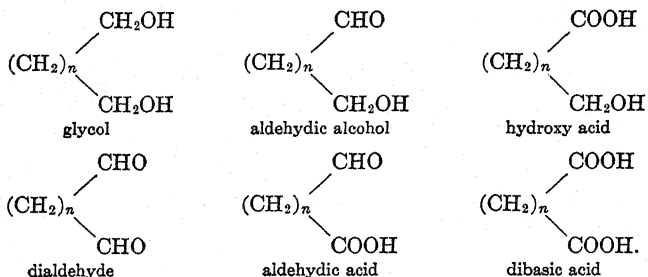
In general the higher polyhydric alcohols are sweet, crystalline compounds, readily soluble in water. Their reactions are those which would be predicted from a knowledge of the simpler polyhydric alcohols. Thus on acylation with acetic anhydride, the pentahydric alcohols form pentacetates, the hexahydric alcohols, hexacetates. The close relationship of these higher polyhydric alcohols to the sugars will be evident later (Chap. XVII).

#### OXIDATION PRODUCTS OF THE GLYCOLS

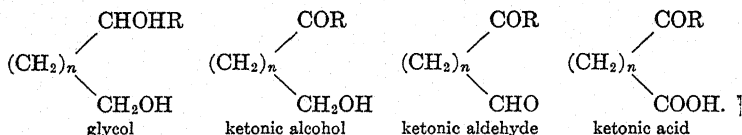
**Classification.** By the oxidation of the monohydric alcohols ( $ROH$ ), one obtains an aldehyde or ketone and eventually an acid, if the alcohol is primary. In the same way, the oxidation of the glycols (dihydric alcohols) will yield compounds containing the carbonyl group, and acids will be obtained as the final product if the group  $-CH_2OH$  is originally present in the molecule.

The following classes of compounds are the possible oxidation

products of a glycol with two primary groups (in the case of ethylene glycol,  $n = 0$ ):



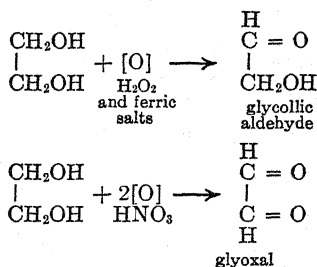
If the glycol contains both a primary and a secondary group, the following are the possible oxidation products:



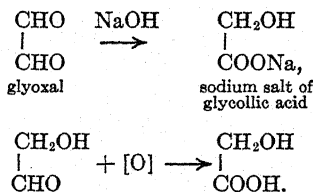
The oxidation products of a glycol which has two secondary alcohol groups would be a ketonic alcohol or a **diketone**,  $\text{RCO}-(\text{CH}_2)_n\text{COR}$ . A ditertiary alcohol would have no oxidation products which contained the same number of carbon atoms. As in the case of a simple tertiary alcohol, the oxidation of such a compound would immediately disrupt the molecule.

Many representatives of all the classes of compounds just outlined are known. In most cases there are more convenient methods of preparing them than by the oxidation of the glycols, but this fact does not, of course, alter their relationship to each other and to the glycols. The dibasic acids are so important that the whole of the next chapter will be devoted to them. Those compounds in which there are two carbonyl groups, or a carbonyl group and a carboxyl group separated by one carbon atom, have very special and peculiar properties. Such compounds are the **beta diketones** (or 1, 3-diketones),  $\text{RCOCH}_2\text{COR}$ , and the **beta ketonic acids**,  $\text{RCOCH}_2\text{COOH}$ . A special chapter will be devoted to these compounds and their peculiarities. Of the remaining types only a few representatives related to ethylene glycol or propylene glycol are of sufficient general interest to be included in this elementary survey of the carbon compounds.

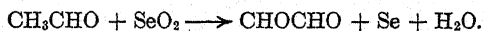
**Glycollic Aldehyde and Glyoxal.** These two compounds are the first oxidation products of ethylene glycol. The one or the



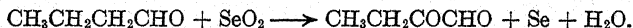
other is formed depending on the nature of the oxidizing agent. When treated with alkali, glyoxal undergoes an *internal* Cannizzaro reaction (p. 128). In this interesting reaction one aldehyde group is oxidized to an acid group and the other reduced to a primary alcohol. The product is the sodium salt of a hydroxy acid, **glycollic acid**; the free acid is also formed by the careful oxidation of glycollic aldehyde:



**Glyoxal** is best prepared from acetaldehyde by heating with selenium dioxide:



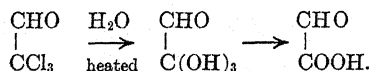
This oxidation reaction is applicable to all aldehydes and ketones which have the linkage  $-\text{CH}_2\text{C} = \text{O}$ . Thus, with butyraldehyde a similar oxidation occurs:



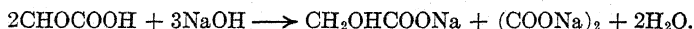
It should be noticed that the hydrogens of the alpha carbon atom are attacked and not the hydrogen attached to the easily oxidized carbonyl group. This remarkable reaction must be connected in some way with the peculiarities of the alpha carbon atom which we have previously discussed (p. 118).

Glyoxal exists in several polymeric modifications. The pure compound is a green gas with a pronounced irritating odor. In water solution it is hydrated and exists probably entirely as  $\text{CHOCH}(\text{OH})_2$ . Several solid polymers are known which are formed on evaporating the solution. Both glyoxal and glycollic aldehyde react with the usual reagents which are used for characterizing aldehydes and ketones.

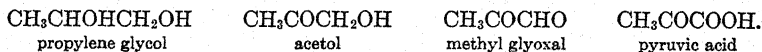
**Glyoxylic Acid,  $\text{CHOCOOH}$ ,** is the aldehydic acid corresponding to ethylene glycol. It is formed by the oxidation of ethylene glycol or better glycollic acid, or by the slow hydrolysis of chloral (p. 125) with water at an elevated temperature:



Glyoxylic acid is hydrated and the anhydrous form is not known. Its formula should therefore probably be written  $\text{CH}(\text{OH})_2\text{COOH}$ . In water solution it shows the typical reactions of an aldehyde. On treatment with alkali it undergoes the Cannizzaro reaction forming glycollic acid and oxalic acid:



**Pyruvic Acid.** The oxidation products of propylene glycol,  $\text{CH}_3\text{CHOHCH}_2\text{OH}$ , are the simplest representatives of the ketonic alcohols, aldehydes, and acids ( $n = 0$  in the second classification on p. 192). Pyruvic acid,  $\text{CH}_3\text{COCOOH}$ , is thus to be regarded as the final member of the following series:



Although each member of this group may be prepared from propylene glycol, by an oxidation process (or series of processes), it is more convenient to prepare them by special methods. For example, pyruvic acid is conveniently prepared by heating racemic tartaric acid (p. 226); hence it is often called **pyroracemic acid**; the reaction involved is complicated. Pyruvic acid is a substance of considerable importance to the biochemist, since it is probably an intermediate product in the changes which sugars undergo in the animal organisms.

Pyruvic acid is a liquid boiling at  $165^\circ$  and solidifying at  $14^\circ$ . It has an irritating odor. It is miscible in water in all proportions. Although it contains no aldehyde group or secondary alcohol group, it is easily oxidized with the evolution of carbon

dioxide. For this reason it reduces an ammoniacal solution of silver nitrate:



### QUESTIONS AND PROBLEMS

1. Write balanced equations showing: (a) two general methods of preparing glycols; (b) the saponification of tristearin; (c) the hydrogenation of triolein.
2. How do the following differ chemically: a lubricating oil, oil of wintergreen, cottonseed oil, linseed oil, beeswax, tallow? What are the industrial uses of the last four?
3. What simple method could you employ to decide whether a certain oil was a vegetable oil or a petroleum product?
4. Describe briefly the methods now employed for preparing "stearin" and soap from cottonseed oil. What important substance is a by-product? For what is it used?
5. Write structural formulas for: tripalmitin, methyl butyrate, oleic acid, isopropyl formate, nitroglycerine, propyl propionate, ethylene oxide, 1, 4-dioxane, trimethylene glycol.
6. A certain oil is known to be either a vegetable oil or a mixture of a mineral oil and tallow. How could you decide between the two possibilities? By what experiments would it be possible to distinguish (a) cottonseed oil from a mixture of tallow and linseed oil; (b) butter from a mixture of lard and cottonseed oil; (c) a stearic acid candle from a paraffin candle?
7. What peculiar properties has a "drying oil"? For what are such oils used?
8. Write equations showing: (a) the preparation of pinacol; (b) the oxidation of pyruvic acid; (c) three reactions of ethylene oxide of industrial importance; (d) the preparation of glyoxal; (e) an example of an internal Cannizzaro reaction; (f) the rearrangement of pinacol to pinacolone.
9. Write structural formulas illustrating the following terms: a glyceride, a beta ketonic acid, a 1, 3-diketone, a chlorohydrin, a 1, 4-glycol.
10. Compare the structural formulas and chemical and physical properties of the following natural products: lecithin, carnauba wax, triolein, arabitol, tristearin.

## CHAPTER X

### DIBASIC ACIDS

A variety of organic acids have been isolated from plants and fruits. These are for the most part acids with two carboxyl groups (dibasic acids), or with a hydroxyl group in addition to the carboxyl group (hydroxy acids). We shall consider these compounds in this and the following chapter. A few of these acids are relatively inexpensive because they can be readily manufactured from natural sources or prepared synthetically. They are used in the laboratory and in the industry for a number of different purposes.

#### DIBASIC ACIDS

Acids which have two replaceable hydrogen atoms are called dibasic acids. An homologous series of dibasic acids starts with **oxalic acid**,  $(\text{COOH})_2$ , and may be represented by the general formula  $(\text{CH}_2)_n(\text{COOH})_2$ . The first nine members are listed below:

#### DIBASIC ACIDS

NAME	FORMULA	MELTING POINT	SOLUBILITY GRAMS PER 100 GRAMS OF WATER AT 20°
Oxalic	$(\text{COOH})_2$	189°*	8.7
Malonic	$\text{HOOCCH}_2\text{COOH}$	136°	74
Succinic	$\text{HOOCCH}_2\text{CH}_2\text{COOH}$	181°	6
Glutaric	$\text{HOOCCH}_2\text{CH}_2\text{CH}_2\text{COOH}$	98°	64
Adipic	$\text{HOOC}(\text{CH}_2)_4\text{COOH}$	153°	2
Pimelic	$\text{HOOC}(\text{CH}_2)_5\text{COOH}$	105°	5
Suberic	$\text{HOOC}(\text{CH}_2)_6\text{COOH}$	144°	0.2
Azelaic	$\text{HOOC}(\text{CH}_2)_7\text{COOH}$	106°	0.3
Sebacic	$\text{HOOC}(\text{CH}_2)_8\text{COOH}$	134°	0.1

\* Anhydrous acid; the hydrate loses its water at about 100°.

**General Properties.** All these acids form *two types of salts*, neutral salts and acid salts. For example, potassium oxalate  $(\text{COOK})_2$  and acid potassium oxalate  $\text{HOOCCOOK}$ . It will be

noticed that, unlike most of the simple compounds hitherto studied, these substances are solids. As would be expected from the predominance of the carboxyl groups, the lower members are soluble in water.

The melting points and solubility in water show an alternation as we proceed up the series. This is shown by the values in the table and in Fig. 21. The acids with an even number of carbon atoms are higher melting and have a lower solubility; with increase in molecular weight the melting point decreases. The

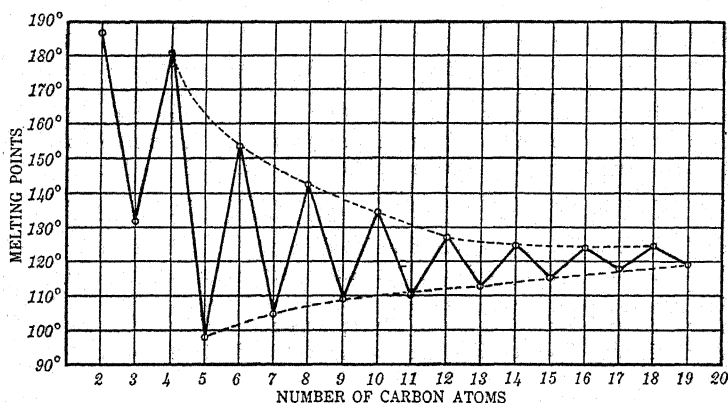


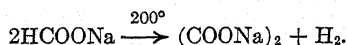
Fig. 21. The melting points of the dibasic acids,  $(\text{CH}_2)_n(\text{COOH})_2$ .

melting points of the acids with an odd number of atoms at first decrease and then increase. The two series finally appear to converge. This complex relationship is different from the regular and gradual increase in boiling points so often noted in other series. As a general rule, the melting points of organic compounds do not show the same regular change in an homologous series as do the boiling points.

#### *Oxalic Acid*

**Preparation of Sodium Oxalate.** The first member of the series occurs in many plants, usually as the acid potassium salt. Thus, both rhubarb and sorrel contain considerable quantities of oxalates. The acid has been an article of commerce for many years. Its sodium salt was formerly prepared by fusing sawdust with a mixture of sodium and potassium hydroxides and leaching

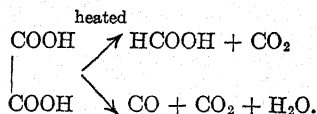
out the sodium oxalate from the partially charred mass. Evaporation of the solution yielded sodium oxalate. The modern method consists in heating sodium formate to  $200^{\circ}$ ; at this temperature hydrogen is evolved.



Sodium formate is prepared from sodium hydroxide and carbon monoxide (p. 85). Thus, the modern industrial synthesis of sodium oxalate is essentially *a synthesis from coal and sodium hydroxide*.

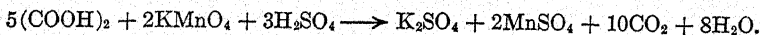
**Preparation of Soluble Non-Volatile Acids from Salts.** To obtain the free acid from the sodium salt, it is necessary to proceed in a special manner which we have not hitherto encountered. Oxalic acid can not be distilled without decomposition; it is soluble in water and insoluble in such solvents as ether and chloroform. Because of these physical properties the usual methods of obtaining an acid from its salts can not be employed (p. 81). Therefore, the calcium salt is prepared by adding lime to an aqueous solution of sodium oxalate. Calcium oxalate is insoluble and precipitates. The precipitate is filtered off and treated with the calculated quantity of dilute sulfuric acid. Calcium sulfate and oxalic acid are formed; the former, being insoluble, can be filtered off. Oxalic acid crystallizes from the filtrate on evaporation. A similar procedure must be adopted in preparing acids from salts in every case in which the acid is soluble in water and can not be distilled or extracted from the solution.

**Chemical Behavior of Oxalic Acid.** Oxalic acid crystallizes with two molecules of water, which it loses when heated to  $100^{\circ}$ . The anhydrous acid sublimes with partial decomposition above  $150^{\circ}$ . On rapid heating the decomposition is complete, the products being formic acid, carbon dioxide, carbon monoxide, and water:



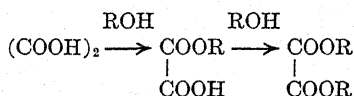
In the presence of sulfuric acid the decomposition takes place rapidly when the mixture is slightly warmed; carbon monoxide, carbon dioxide, and water are the products.

Oxalic acid like formic acid is easily oxidized to carbon dioxide and water. In acid solution potassium permanganate is reduced to manganous salts by oxalates:



This reaction is often used in quantitative analysis. Large quantities of oxalic acid and its salts are used in laundry work for removing iron stains and ink spots. Oxalic acid is oxidized by the ferric compounds, and they in turn are reduced to the more soluble ferrous salts.

The characteristic reactions of the fatty acid series are also typical of the dibasic acids. Thus, oxalic acid when treated with phosphorus pentachloride forms the acid chloride, *oxalyl chloride*,  $\text{ClCOCOCl}$ . When heated with an alcohol, first one carboxyl group and then the other is esterified. The compounds which have one unesterified carboxyl group are usually designated as



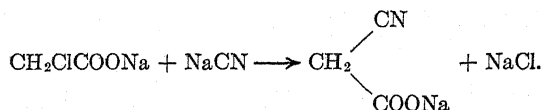
**acid esters**; those in which the esterification is complete, neutral esters. Since the latter are the most common representatives of the esters of dibasic acids, they are usually named without any prefix to indicate the number of ester groups. Thus **ethyl oxalate** is  $\text{C}_2\text{H}_5\text{OOC}\text{COOC}_2\text{H}_5$ , the neutral ester.

The alkali metal salts and the ammonium salts of oxalic acid are somewhat soluble in water. None of these compounds are very soluble, however; thus one of the most soluble, ammonium acid oxalate,  $(\text{NH}_4\text{HC}_2\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O})$ , dissolves only to the extent of 1 part in 16 parts of water at  $12^\circ$ . The diammonium and disodium salts are only about half as soluble as this, and the sodium and potassium acid salts are only sparingly soluble in cold water. A peculiar compound, potassium tetraoxalate,  $\text{KHC}_2\text{O}_4 \cdot \text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ , readily crystallizes on cooling an aqueous solution of potassium oxalate and oxalic acid in the correct proportions. This salt is often used as a standard in analytical chemistry since it can be readily purified by crystallization. The oxalates of the alkaline earths are very little soluble in water, calcium oxalate being particularly insoluble (5 milligrams per liter at  $18^\circ$ ); they dissolve in mineral acids since oxalic acid is somewhat weaker than the very strong acids.

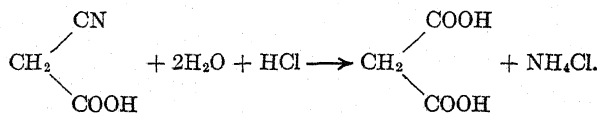
Oxalic acid is a surprisingly strong acid; the value of  $K_A$  is  $9 \times 10^{-2}$ . Its position in the diagram shown on p. 83 would be just above dichloroacetic acid. The next member of the series, malonic acid, is much weaker,  $K_A = 1.6 \times 10^{-3}$  (the position of chloroacetic acid on the diagram); the higher members of the series are only slightly stronger than acetic acid. (Succinic acid,  $K_A = 6.9 \times 10^{-5}$ , glutaric acid,  $K_A = 5.3 \times 10^{-5}$ , adipic,  $K_A = 4.2 \times 10^{-5}$ , pimelic,  $K_A = 3.4 \times 10^{-5}$ , as compared with acetic of  $1.86 \times 10^{-5}$ .)

*Malonic Acid*

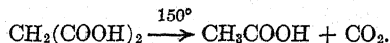
**Preparation from Chloroacetic Acid.** Malonic acid is prepared by a series of reactions starting with acetic acid. These illustrate several general principles in regard to the synthesis of complex acids. The first step is the preparation of **chloroacetic acid** (p. 100). The sodium salt of chloroacetic acid reacts with sodium cyanide exactly like an alkyl halide; the product is the sodium salt of the half nitrile of malonic acid (**cyanoacetic acid**):



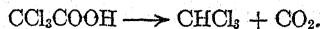
This nitrile on hydrolysis yields malonic acid:



**Loss of Carbon Dioxide on Heating.** Like oxalic acid, malonic acid loses carbon dioxide on heating. In this case the other product is acetic acid:

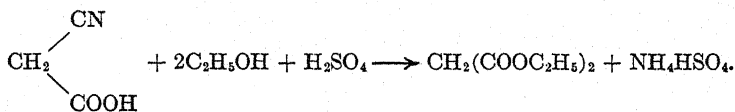


The simple fatty acids and the higher members of the dibasic acid series do not decompose in this way on heating. As a rule the carboxyl group is a stable arrangement of atoms and does not undergo a change even at 200°. The presence of certain kinds of atoms or groups on the carbon atom holding the carboxyl group, however, alters this situation. Three halogen atoms have much the same influence as an additional carboxyl group; trichloroacetic acid,  $\text{CCl}_3\text{COOH}$ , loses carbon dioxide rapidly on boiling its water solution:



**Malonic Esters.** The esters of malonic acid, for example, **ethyl malonate**,  $\text{CH}_2(\text{COOC}_2\text{H}_5)_2$ , are extensively used in the synthesis of compounds in the laboratory. A consideration of such syntheses involves, however, a discussion of the peculiar

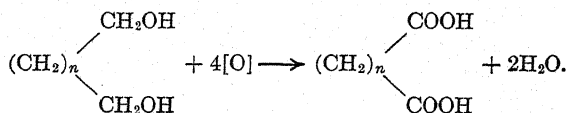
properties of certain esters and will be postponed until Chap. XIII. Malonic esters are prepared directly from cyanoacetic acid by boiling it with alcohol and acid:



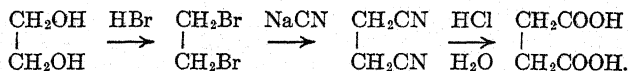
### THE HIGHER DIBASIC ACIDS

Oxalic acid and malonic acid differ from the other members of the dibasic acid series in some of their reactions and in their method of preparation. The other members of the series have similar chemical properties and may be all prepared by the same general methods.

**General Methods of Preparation.** The dibasic acids may be prepared by oxidizing the corresponding glycols. In a general form we may express this fact by the following equation:



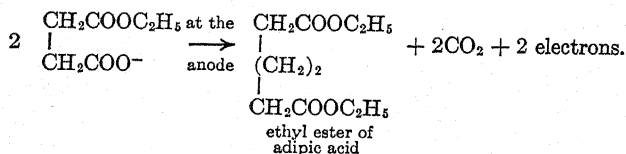
The dibasic acids are conveniently prepared from the glycols with *two less* carbon atoms by the preparation of the dibromide, the dinitrile, and hydrolysis. This method is illustrated by the synthesis of succinic acid from ethylene glycol:



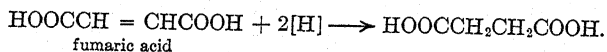
The Grignard method of preparing acids from the corresponding halides can be used for preparing dibasic acids. The dihalides above trimethylene bromide react with magnesium in absolute ether to form dimagnesium derivatives which combine with two moles of carbon dioxide. When this sequence of reactions is applied to 1, 5-dibromopentane, 50 per cent yield of pimelic acid is obtained.

The electrolysis of the acid esters of the dibasic acids provides a method of nearly doubling the length of the chain. By this method a number of dibasic acids of very high molecular weight have been prepared; the yields are often rather poor, however.

As an example, the preparation of adipic ester from the acid ester of succinic acid may be given:



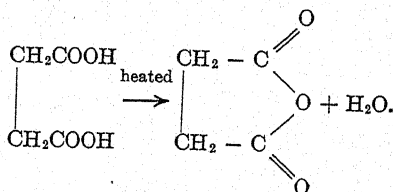
**Succinic Acid.** This is the only one of the higher dibasic acids which is a common substance. It occurs in amber (a fossil gum), and was originally prepared by the distillation of this material. It has been isolated from a variety of plants, certain animal tissue, and the urine of animals. It seems to play an important role in the plant and animal life since it is widely distributed, but its biochemical mode of formation is not entirely clear. It may be prepared from ethylene glycol by the series of reactions outlined in the preceding paragraph. It is prepared industrially by the electrolytic reduction of fumaric acid (p. 284):



#### CYCLIC ANHYDRIDES

Succinic acid and glutaric acid differ from all the other members of the series  $(\text{CH}_2)_n(\text{COOH})_2$ , by the fact that they readily form *cyclic anhydrides*. This may be illustrated by the preparation of succinic anhydride.

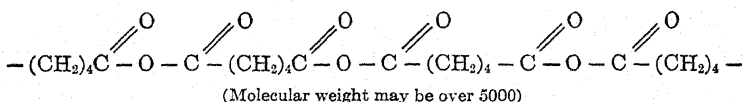
**Succinic Anhydride.** Succinic anhydride,  $(\text{CH}_2\text{CO})_2\text{O}$ , is a white, crystalline solid (m.p.  $120^\circ$ ) obtained by heating succinic acid alone or with dehydrating agents such as acetic anhydride or phosphorus oxychloride ( $\text{POCl}_3$ ):



This anhydride differs from acetic anhydride in that the two acyl groups are part of the same molecule. Obviously such cyclic anhydrides can be formed only from polybasic acids.

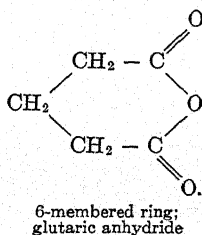
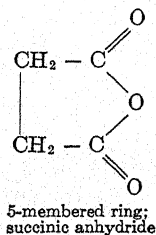
**Dehydration of Dibasic Acids.** Oxalic acid on dehydration decomposes into carbon monoxide and dioxide while malonic acid yields a gas carbon suboxide  $O = C = C = C = O$  instead of a cyclic anhydride. Adipic acid and the higher acids on dehydration first yield an anhydride of high molecular weight.

It should be noticed that in the dehydration of dibasic acids, water may be lost in several ways. Dehydration may occur within one molecule to form a cyclic anhydride (as in the case of succinic and glutaric acids) or between two or more molecules. The latter process may continue so that many molecules participate to give a long chain anhydride. Such compounds obtained from adipic acid by dehydrating agents may be formulated as follows:



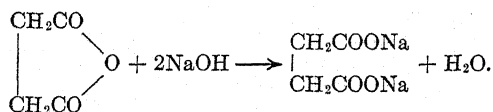
By heating in a very high vacuum, these substances can be broken down to the cyclic anhydride. The cyclic anhydrides of the dibasic acids above glutaric, however, are quite unstable. When they are treated with small amounts of strong acids as catalysts, they readily revert into the form with a high molecular weight. The anhydrides of high molecular weight are usually called polymers although originally this term was limited to such cases as that of formaldehyde, where the simple compound and the complex compounds have the same empirical formulas. Since the basic structure of the polymer of formaldehyde (p. 113) and the anhydrides of high molecular weight is the same, the use of the term polymer has been extended. We now recognize two classes of polymers: (1) those in which the large molecule is built up by the additive combination of the monomer (paraformaldehyde, rubber) and (2) those in which the condensation of the molecules to form long chains involves the elimination of water.

The peculiar behavior of succinic and glutaric acids is connected with the fact that the ring in their anhydrides contains five and six atoms. In general we shall find that compounds containing five- and six-membered rings are usually more easily prepared than those with larger or smaller ring systems.

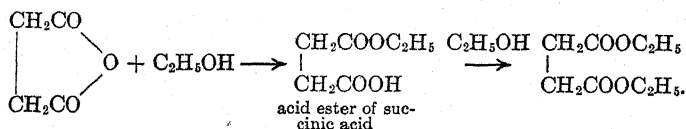


Some of the dibasic acids which may be regarded as derivatives of succinic acid or glutaric acid also form anhydrides, though this is not invariably the case. Thus no cyclic anhydride can be obtained directly from the chloro or bromosuccinic acids. On the other hand, the alkyl derivatives readily form anhydrides.

**Reactions of Cyclic Anhydrides.** In their reactions the cyclic anhydrides closely resemble the simple acid anhydrides. They are hydrolyzed by water with the formation of the corresponding acid; alkali is usually needed to catalyze this reaction and in a few cases to complete it:



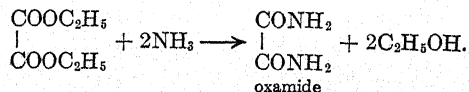
With alcohol an acid ester is formed which on further boiling with alcohol yields the neutral ester:



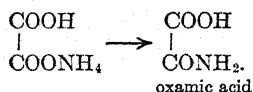
### AMIDES OF DIBASIC ACIDS

The general method of preparation of the amides of the dibasic acids follows the reactions outlined in connection with a consideration of the amides of the fatty acid. Succinic acid and glutaric acid occupy an exceptional place, as here cyclic compounds known as cyclic imides may be formed.

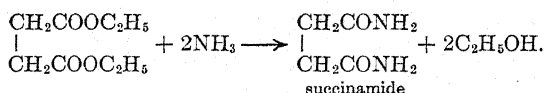
**Oxamide and Oxamic Acid.** The diamide of oxalic acid, oxamide,  $(\text{CONH}_2)_2$ , is a white crystalline powder, insoluble in water and alcohol. It sublimes on heating with partial decomposition. It can be formed by the action of ammonia on ethyl oxalate or by heating ammonium oxalate:



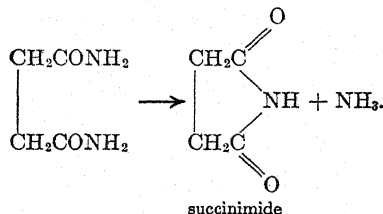
The acid amide of oxalic acid,  $\text{HOOC}\text{CONH}_2$ , is known as oxamic acid. It is both an amide and an acid. It is prepared by heating ammonium acid oxalate:



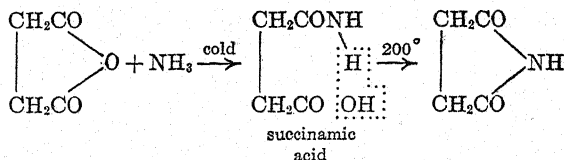
**Succinamide and Succinimide.** The diamide of succinic acid,  $(\text{CH}_2)_2(\text{CONH}_2)_2$ , is a crystalline solid which is formed by the action of ammonia on ethyl succinate:



When succinamide is heated it loses ammonia and forms the cyclic compound known as **succinimide**. This is a crystalline solid melting at  $126^\circ$  and readily soluble in water.



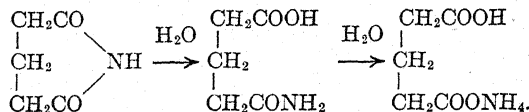
Succinimide may also be formed from succinic anhydride by the following reactions:



The isolation of the intermediate (succinamic acid) is not necessary if the reaction is carried out at high temperatures. **Glutarimide** is prepared in a manner similar to succinimide.

The cyclic imides on boiling with aqueous acids or bases are

hydrolyzed with the formation of the acid and ammonia. The first product of the hydrolysis is the acid amide which can be isolated under suitable conditions:



The presence of two acyl groups on the nitrogen atom of succinimide makes the hydrogen atom more acidic than in a simple amide. Although the compound is neutral in water solutions, it will readily form a sodium or potassium salt. Such salts of the cyclic imides are somewhat hydrolyzed by water but not decomposed by alcohol (except slowly as the alcohol causes the opening of the ring).

### QUESTIONS AND PROBLEMS

- Outline the procedures for obtaining the free acids from the potassium salts of oxalic and propionic acid. Explain reasons for the procedures you propose.
- Outline the synthesis of the following: (a) oxalic acid from the elements; (b) malonic ester starting with calcium carbide; (c) glutaric acid from glycerol; (d) glutaric acid from succinic acid.
- Write balanced equations for the following reactions: (a) oxalyl chloride and ethyl alcohol; (b) malonic acid heated; (c) glutaric anhydride and ammonia; (d) succinimide and ethyl alcohol; (e) hydrolysis of glutarimide; (f) ethyl oxalate and ammonia.
- Compare the preparations and chemical properties of propionamide, oxamide, and succinimide. To what is due the increased acidity of the latter compound as compared to amides?
- (a) Outline the general methods of preparing the dibasic acids; (b) indicate by equations the action of dehydrating agents on the dibasic acids of the homologous series up to pimelic acid.
- Write equations showing *all* the steps in the preparation of crystalline oxalic acid from carbon monoxide and sodium hydroxide.
- A certain acid is decomposed on heating, is very soluble in water but insoluble in organic solvents. Devise a method of preparing it from its sodium salt if the lead salt is insoluble in water.
- Write equations illustrating what you think would happen if you heated the following solids above their melting points:  $\text{CH}_3\text{CH}(\text{COOH})_2$ ,  $\text{CH}_2\text{CH}(\text{COOH})\text{CH}_2\text{COOH}$ .
- Compare the action of dehydrating agents on oxalic acid and succinic acid.

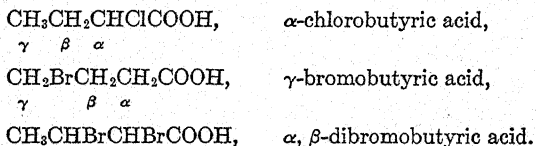
## CHAPTER XI

### HYDROXY ACIDS

One or more hydrogen atoms of the fatty acids or of the dibasic acids may be replaced by hydroxyl groups. The resulting compounds are known as **hydroxy acids**. They are both acids and alcohols and in general have the reactions of both classes of compounds. A number are of commercial importance, and of interest to the biochemist as they occur in plants and animals. It will be recalled that there is no method for directly substituting a hydrogen atom of a paraffin hydrocarbon by an hydroxyl group. Similarly we find that the hydroxy acids can not be prepared directly from the fatty acids. The preparation of the hydroxy acids usually proceeds from the corresponding halogen compounds — chloro or bromo acids. We shall, therefore, first consider these classes of substances (which are of minor importance by themselves), and then turn to the hydroxy acids which may be prepared from them.

#### HALOGEN-SUBSTITUTED ACIDS

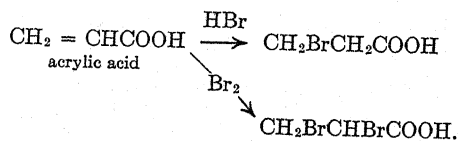
**Classification and Nomenclature.** The methods of preparation and reactions of the acids containing a halogen atom differ according to the position of the atom. It is usual to indicate the position of an atom or group in a substituted fatty acid by means of a Greek letter. The lettering starts with the *carbon atom next to the carboxyl group*. The method is illustrated by the following examples:



In the case of dibasic acids, it is common practice to designate the two carbon atoms next to the two carboxyl groups as  $\alpha$  and  $\alpha'$  and continue the lettering in the two directions until they meet.

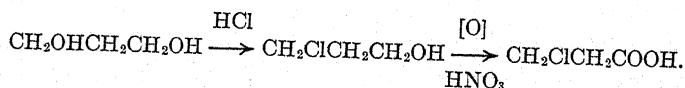
Thus,  $\text{HOCCBr}_2\text{CH}_2\text{COOH}$  is  $\alpha$ ,  $\alpha$ -dibromosuccinic acid and  $\text{HOCCCHBrCHBrCOOH}$  is  $\alpha$ ,  $\alpha'$ -dibromosuccinic acid.

**Preparation of Bromo and Chloro Acids.** The preparation of alpha halogen acids from the fatty acids has already been considered (p. 100). Beta halogen acids may often be prepared by the addition of halogen acids to unsaturated acids, while  $\alpha$ ,  $\beta$ -dibromo or dichloro (but *not* diiodo) acids are formed by the addition of bromine or chlorine to the same acid. The behavior of acrylic acid (p. 279) will suffice as an example.



It should be noted that this addition is contrary to Markownikoff's rule which applies only to hydrocarbons. The halogen atom always goes to the  $\beta$  position when acids containing the linkage  $\text{C}=\text{C}-\text{COOH}$  react with halogen acids (see further, p. 280).

Acids containing halogen in the  $\beta$  or  $\gamma$  position may also be prepared from the glycols, which in turn may be synthesized by a variety of methods (p. 178). The preparation of  $\beta$ -chloropropionic acid from trimethylene glycol is an illustration of this method:



Beta halogen acids readily lose a molecule of halogen acid, forming the unsaturated acid. As this reaction is more rapid than most metathetical processes, it is difficult to substitute the halogen atom in the beta position with other atoms or groups.

Halogen acids having the substituent atom on the end of the chain are sometimes known as **omega ( $\omega$ ) halogen acids**. They may be prepared from the corresponding chloro or bromohydrins.

**Physical Properties.** The physical properties of some of the simpler halogen substitution products of the fatty acids are given in the accompanying table. The alpha halogen acids and their esters have a marked physiological action. The esters of the alpha-substituted acids are lachrymatory substances like the halogenated aldehydes and ketones. Trichloroacetic acid is used in medicine as a corrosive agent for removing the outer tissues as required in the treatment of corns and warts. (It is manufactured by the cautious oxidation of chloral.)

PHYSICAL PROPERTIES OF SOME CHLORO-, BROMO-, AND IODO-  
ACIDS AND ESTERS

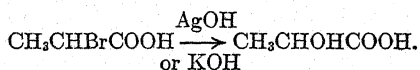
NAME	FORMULA	MELT- ING POINT	BOIL- ING POINT
Chloroacetic acid	$\text{CH}_2\text{ClCOOH}$	62°	189°
Bromoacetic acid	$\text{CH}_2\text{BrCOOH}$	50°	208°
Iodoacetic acid	$\text{CH}_2\text{ICOOH}$	83°	
Dichloroacetic acid	$\text{CHCl}_2\text{COOH}$	11°	194°
Trichloroacetic acid	$\text{CCl}_3\text{COOH}$	55°	200°
$\alpha$ -chloropropionic acid	$\text{CH}_3\text{CHClCOOH}$		186°
$\beta$ -chloropropionic acid	$\text{CH}_2\text{ClCH}_2\text{COOH}$	41°	204°
Halo esters			
Ethyl chloroacetate	$\text{CH}_2\text{ClCOOC}_2\text{H}_5$		144°
Ethyl dichloroacetate	$\text{CHCl}_2\text{COOC}_2\text{H}_5$		158°
Ethyl trichloroacetate	$\text{CCl}_3\text{COOC}_2\text{H}_5$		168°

The influence of a halogen atom in the alpha position on the strength of the acid is very marked. Trichloroacetic acid is nearly as strong as hydrochloric acid in water solution. The mono and dichloro acetic acids are not so strong (see diagram, p. 84).

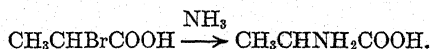
If the halogen atom is removed from the carboxyl group by one or more atoms the effect on the dissociation constant is very slight.

**Reactions of Alpha Halogen Acids.** A halogen atom in the alpha position to a carboxyl group is readily replaced by a variety of groups. In general, the rate of such metathetical reactions is considerably more rapid than with the alkyl halides themselves. The esters of the  $\alpha$ -halogen acids enter into exactly the same type of metathetical reactions. The following reactions of  $\alpha$ -bromopropionic acid will illustrate the common and useful reactions:

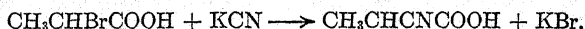
(a) *Preparation of hydroxy acid:*



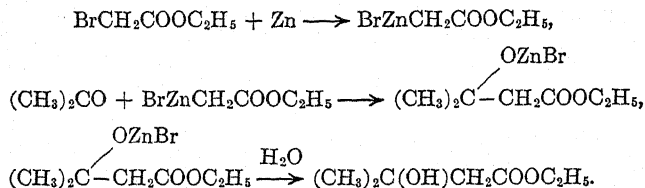
(b) *Preparation of amino acid:*



(c) *Preparation of cyano acid* (half nitrile of a substituted malonic acid):



A Grignard reagent can not be prepared from the halogen-substituted acids or their esters whether the halogen be in the alpha or any other position. The *alpha* bromo esters, however, form an *organo-zinc* compound similar to a Grignard reagent. This compound will add to the carbonyl group of aldehydes and ketones but not of esters. This is known as the **Reformatsky reaction**. It may be illustrated by the following example:



### HYDROXY ACIDS

The important hydroxy acids which occur in nature are listed in the table which follows.

SOME IMPORTANT HYDROXY ACIDS

NAME	FORMULA	OCCURRENCE
Malic acid	$\begin{array}{c} \text{CHOHCOOH} \\   \\ \text{CH}_2\text{COOH} \end{array}$	Unripe fruits, gooseberries, rhubarb stalks, unripe grapes, cherries, tomatoes.
Lactic acid	$\text{CH}_3\text{CHOHCOOH}$	Sour milk, in muscle after activity, beet molasses, in blood and urine.
Citric acid	$\begin{array}{c} \text{CH}_2\text{COOH} \\ / \quad \backslash \\ \text{COH}(\text{COOH}) \\ \backslash \quad / \\ \text{CH}_2\text{COOH} \end{array}$	All citrus fruits.
Glycollic acid	$\text{CH}_2\text{OHCOOH}$	Chief acid constituent of sugar cane; present in beet juice; unripe grapes.
Tartaric acid	$\begin{array}{c} \text{CHOHCOOH} \\   \\ \text{CHOHCOOH} \end{array}$	Argol (in wine casks) (monopotassium salt).
Beta hydroxybutyric acid	$\begin{array}{c} \text{CH}_3\text{CHOH} \\   \\ \text{CH}_2\text{COOH} \end{array}$	Urine from those suffering with diabetes.

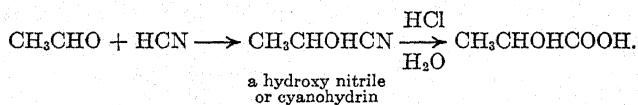
**Nomenclature.** The acids listed above, with one exception, have the hydroxyl group adjacent to a carboxyl group; they are called **alpha hydroxy acids**. The position of a hydroxyl group like that of a halogen atom is indicated by a Greek letter.

**Synthesis.** The synthetic production of *alpha hydroxy acids* in the laboratory is possible by two different procedures which are illustrated by the synthesis of  $\alpha$ -hydroxypropionic acid, — lactic acid.

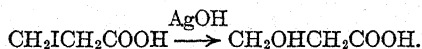
(1) We may start with the alpha chloro acid and replace the chlorine atom with hydroxyl:



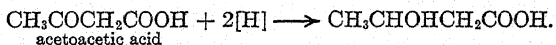
(2) We may start with an aldehyde, add hydrocyanic acid (p. 211) and then hydrolyze the hydroxy nitrile:



The *Beta and Gamma hydroxy acids* may be readily prepared from the corresponding halogen compounds. For example,  $\beta$ -hydroxypropionic acid, hydracrylic acid, may be prepared from  $\beta$ -iodopropionic acid:



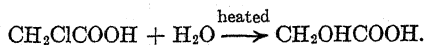
Hydroxy acids may also be prepared by the reduction of the corresponding keto acid if this is available. This method is illustrated by the preparation of  $\beta$ -hydroxybutyric acid from acetoacetic acid:



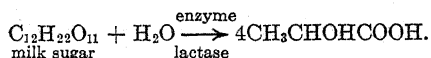
The use of the Reformatsky reaction in the synthesis of beta hydroxy esters has been mentioned above (p. 210). The hydroxy acids are readily obtained from the esters by hydrolysis.

**Glycollic Acid.** The simplest representative of the hydroxy acids occurs in unripe fruits. It is a crystalline solid melting at

80° and very soluble in water. It may be prepared by the action of dilute alkali on monochloroacetic acid or by merely boiling a solution of this acid with water:



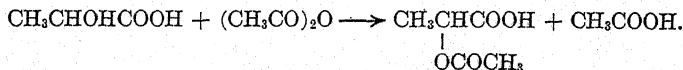
**Lactic Acid.** Lactic acid,  $\text{CH}_3\text{CHOHCOOH}$ , is formed when milk sours, according to the following reaction:



For industrial purposes lactic acid is either isolated from sour milk or made by a bacterial fermentation of glucose. It is an oily liquid which is difficult to obtain pure. Two isomeric forms of lactic acid are considered in the next chapter. It is used in dyeing, and its ethyl ester is a commercial solvent.

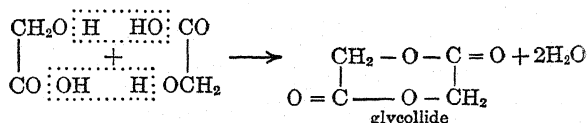
From the point of view of the biochemist, lactic acid is a very important compound. The energy necessary for muscular action appears to be normally supplied by the decomposition of glycogen (p. 316) to lactic acid. Glycogen is a carbohydrate similar to starch; it is stored in the liver and carried by the blood stream to the muscle. A complicated series of reactions are involved in the change of glycogen to lactic acid (p. 314). Following the contraction of the muscle, the lactic acid disappears from the muscle by diffusion into the blood stream and by oxidation.

**Dehydration of Hydroxy Acids.** The general chemical characteristics of hydroxy acids may be said to embody the properties of both an acid and an alcohol. Thus, as acids they form salts with bases and esters with alcohols; for example, sodium lactate is  $\text{CH}_3\text{CHOHCOONa}$ , and ethyl lactate is  $\text{CH}_3\text{CHOHCOOC}_2\text{H}_5$ . As alcohols, they form esters with acids; thus the acetate of lactic acid is formed from lactic acid and acetic anhydride:



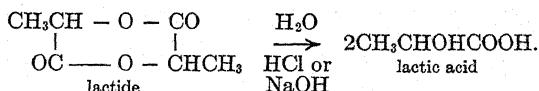
It is obviously an interesting question as to whether a hydroxy acid can form an ester with itself. Such a reaction does, indeed, take place when alpha hydroxy acids are treated with dehydrating agents or merely heated alone for some length of time. The re-

action may be illustrated with glycollic acid, the first member of the series:

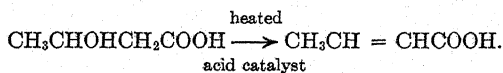


Similarly, lactic acid yields **lactide** on heating. The formation of cyclic double esters is a characteristic of alpha hydroxy acids.

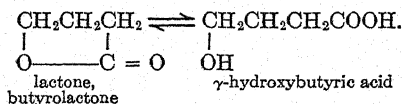
These cyclic esters on hydrolysis regenerate the hydroxy acid:



*Beta hydroxy acids* on heating with dehydrating agents usually lose water with the formation of unsaturated acids:



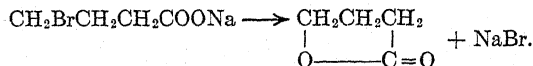
**Lactones.** Gamma hydroxy acids lose water in a very interesting way, yielding cyclic esters formed from only *one* molecule of the acid. These compounds are called **lactones**. They are inner esters, and on hydrolysis yield the hydroxy acid. In the absence of base the reaction is a balanced one; in the presence of alkali the hydrolysis is complete by virtue of the neutralization of the acid:



The point of equilibrium between a lactone and the hydroxy acid is often very favorable to the former, and some gamma hydroxy acids can not be prepared as such. They are known only as salts or esters.

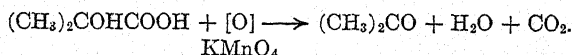
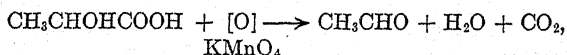
Lactones are also formed from certain delta hydroxy acids but not readily from other hydroxy acids. This fact illustrates the same general rule encountered in connection with the cyclic anhydrides — namely, the ready formation of five or six membered rings. Another method of preparing lactones

is from chloro or bromo acids. Acids having a halogen atom in the  $\gamma$  position form lactones quite rapidly when a solution of their sodium salts stands a short time. This reaction is *not* reversible:



Hydroxy acids under conditions of inner esterification may also form esters between two molecules, or many molecules may esterify each other in such a way that a long chain polyester may result. This is the case with hydroxy acids in which the hydroxyl group is at least 5 carbon atoms removed from the carboxyl group. Thus, 9-hydroxy-nonanoic acid on heating alone or with a catalyst gives polyesters of molecular weights above 5,000. If, however, an extremely dilute solution of an  $\omega$ -hydroxy acid (concentration below .0002 molar in benzene) is dehydrated, large ring lactones can be obtained. It is interesting to note that a very large ring lactone has been found in nature; it is *ambrettolide*, found in certain oils, the lactone ring contains 16 carbon atoms.

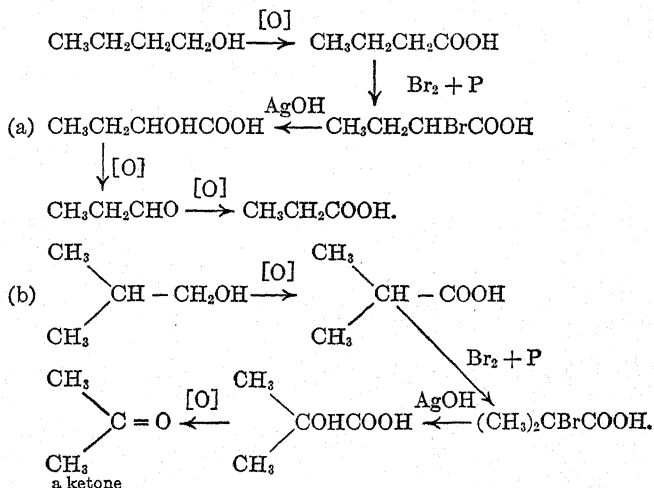
**Oxidation of Alpha Hydroxy Acids.** The alpha hydroxy acids are oxidized more rapidly and at a lower temperature than are secondary or primary alcohols. The reaction involves the loss of carbon dioxide and yields a ketone or aldehyde. Two examples are the following:



**Structure of a Carbon Chain.** The elimination of carbon dioxide from alpha hydroxy acids provides a method of degrading an acid step by step. In this way it is possible to determine the structure of the carbon chain in an acid. This reaction provides one of the best methods of "going down the series," and can also be used for preparative purposes.

As a simple example of the application of this method we may consider the case of the two isomeric primary butyl alcohols. We have already established their structure by certain transformations (p. 138); but the methods there given would not be applicable to all problems of this sort. The step-by-step degradation is a perfectly general method, however. The application of the method involves the preparation of a hydroxy acid through the bromo acid, oxidation, and repetition of the series of reactions

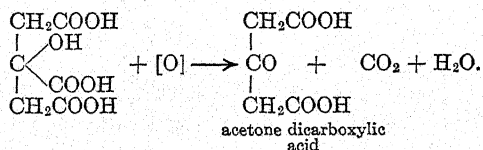
until a known acid or a ketone is the final product of the oxidation. The structure of this ketone shows the position of the branch in the chain. (If an acid is obtained that can not be brominated, this shows a double branch in the chain at this point.)



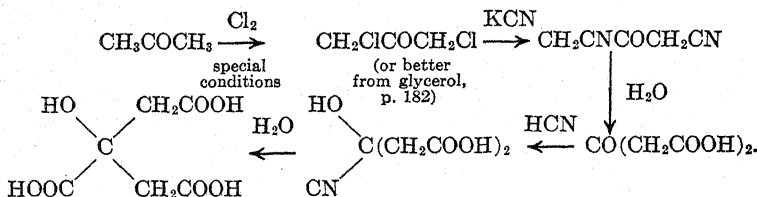
In the actual application of this method it is usually only necessary to remove a few carbon atoms before the product is a substance of known structure which may be identified.

**Citric Acid.** One of the acids most widely distributed in nature is citric acid. It occurs particularly in citrus fruits as the name indicates. It crystallizes with a molecule of water which it loses on heating. The hydrated acid melts at about  $100^\circ$ ; the anhydrous acid at  $153^\circ$ . The acid is very soluble in water. It forms a variety of salts some of which are used in pharmaceutical preparations. The acid itself is widely used in the preparation of beverages. It is prepared either from citrus fruits which are not marketable or by the fermentation of glucose by a certain mold.

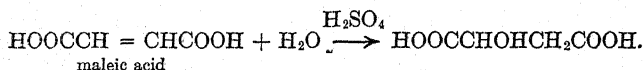
The structure of citric acid follows from its oxidation to acetone dicarboxylic acid:



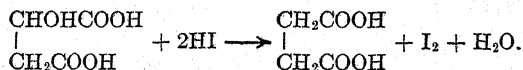
The latter substance may be prepared from dichloroacetone (p. 182), and the complete synthesis of citric acid is thus as follows:



**Malic Acid.** Hydroxysuccinic acid,  $\text{HOOCCHOHCH}_2\text{COOH}$ , is known as malic acid. Like glycollic acid it occurs in unripe fruits. It may be prepared by the action of alkali on chloro- or bromosuccinic acid or by combining maleic acid (p. 284) with water by means of sulfuric acid. This last method is now used for the industrial preparation of malic acid:



The synthetic acid melts at  $130^\circ\text{--}131^\circ$ ; the acid which occurs in nature, at  $100^\circ$ . The two forms also differ in their action on polarized light, the former being without effect while the latter causes a rotation. The structure of both the synthetic and natural acids is established by the fact that on heating with hydrogen iodide they are reduced to succinic acid:



**Tartaric Acid.** Tartaric acid,  $(\text{CHOHCOOH})_2$ , is obtained from the crude potassium acid tartrate, known as *argol*, which crystallizes in wine casks. This salt is probably present in the original wine and separates slowly. When purified by crystallization from water, it is known as *cream of tartar* and is widely used in the manufacture of baking powder.

The tartaric acid of commerce is a white, crystalline solid which melts at  $168^\circ\text{--}170^\circ$ ; it is soluble in water and can not be readily extracted from the solution. In its preparation from *argol*, the insoluble calcium tartrate is first formed by precipitation and is then decomposed with sulfuric acid (compare p. 198). The free acid and its salts are used in dyeing, in medicine, and in the laboratory. Fehling's solution (p. 111) is prepared by adding

sodium hydroxide and a tartrate to dilute copper sulfate solution. The deep blue solution contains a soluble complex cupric tartrate.

**Isomerism of Malic Acid and the Tartaric Acids.** Tartaric acid can be shown by many reactions to be **dihydroxy-succinic acid**. It must be represented by the formula,  $\text{HOOCCHOHC-HOHC-COOH}$ . Yet there are three other compounds which also correspond in their reactions and transformations to the same structure. They are — **laevo tartaric acid** (m.p.  $168^{\circ}$ – $170^{\circ}$ ); **racemic tartaric acid** (m.p.  $205^{\circ}$ – $206^{\circ}$ ); and **meso tartaric acid** (m.p.  $140^{\circ}$ ). (Ordinary tartaric acid (m.p.  $168^{\circ}$ – $170^{\circ}$ ) is called **dextro tartaric acid**.) We have noted above two forms of malic acid; still a third can also be prepared. What is the cause of these cases of peculiar isomerism? The structural theory which we have found so useful, up to this point, gives no clue. According to the rules which have hitherto guided our predictions, there should be one and only one substance of the structure written above. There are actually four. Similarly there should be but one hydroxy succinic acid; three are known.

A number of such exceptional cases came to light from time to time during the rapid growth of organic chemistry in the last half of the nineteenth century. They remained a mystery until van't Hoff<sup>1</sup> and Le Bel<sup>2</sup> in 1874 independently arrived at a solution of the problem. These scientists extended the structural theory to three dimensions, and in this way provided an explanation of these cases of isomerism which were not accounted for by the Kekulé theory. This final step in the completion of the structural theory is described in the next chapter.

### QUESTIONS AND PROBLEMS

1. Write structural formulas for:  $\beta$ -hydroxypropionic acid,  $\alpha$ -hydroxybutyric acid,  $\alpha$ ,  $\beta$ -dibromobutyric acid, cream of tartar, dimethyl tartrate.
2. Outline the steps in the synthesis of  $\alpha$ -hydroxybutyric acid from *n*-propyl alcohol by two different methods.
3. Write the equations for the following reactions: (a) propionic acid, phosphorus tribromide and bromine; (b) sodium salt of  $\gamma$ -hydroxyvaleric acid and hydrogen chloride; (c) dimethyl ester of tartaric acid and acetyl chloride; (d)  $\alpha$ -bromopropionyl bromide and absolute ethyl alcohol.

<sup>1</sup> Jacobus Henricus van't Hoff (1852–1911), Professor at the University of Amsterdam 1877–1896 and at the University of Berlin 1896–1911. He is famous as the joint founder of stereochemistry and for his contributions to the theory of solutions.

<sup>2</sup> Joseph Achille Le Bel (1847–1930), a French chemist who resided in Paris.

4. Outline the steps in the synthesis of the following: (a)  $\text{CH}_3\text{CH}(\text{COOH})_2$  starting with propionic acid; (b)  $\text{CHOH}(\text{COOH})_2$  (tartronic acid) from malonic ester.

5. Discuss lactone formation and hydrolysis, indicating the type of compounds capable of and conditions necessary for such transformations. Explain the statement: "Lactones are inner esters."

6. How would you differentiate between: (a) 3, 3-dimethyl-butanol-1 and 4-methylpentanol-1; (b)  $\text{CH}_3\text{CHClCOOH}$  and  $\text{CH}_3\text{CH}_2\text{COCl}$ ; (c)  $\text{CH}_3\text{CH}_2\text{CHOHCH}_2\text{COOH}$  and  $\text{CH}_2\text{OHCH}_2\text{CH}_2\text{CH}_2\text{COOH}$ ; (d)  $(\text{CH}_3)_2\text{CHCH}_2\text{COOH}$ ,  $(\text{CH}_3)_3\text{CCOOH}$ ,  $\text{CH}_3(\text{CH}_2)_3\text{COOH}$ ?

7. A compound A was obtained having the empirical formula  $\text{C}_6\text{H}_{14}\text{O}$ . On oxidation it gave an acid  $\text{C}_6\text{H}_{12}\text{O}_2$ . On degradation by the reactions outlined in this chapter it gave an acid  $\text{C}_5\text{H}_{10}\text{O}_2$  which was esterified with difficulty and could not be brominated by the usual procedure. What is the structure of A?

8. Indicate steps involved in preparing  $\alpha$ -hydroxyisobutyric acid from isopropyl alcohol;  $\beta$ -hydroxybutyric acid from propylene; isopropyl alcohol from  $\beta$ -methylbutyric acid.

9. What would happen if butyrolactone were treated with: (a) methyl alcohol and sulfuric acid; (b) ammonia gas in anhydrous medium; (c) hydrogen iodide (with heating)?

## CHAPTER XII

### OPTICAL ISOMERISM

**Optical Activity.** Before presenting the theory of van't Hoff and Le Bel mentioned in the preceding chapter, we must discuss briefly the phenomenon known as optical activity. We have seen that two of the four isomeric dihydroxy-succinic acids are called dextro tartaric acid and laevo tartaric acid respectively. The words **dextro** and **laevo** refer to the fact that solutions of these substances have the property of rotating the plane of polarized light — the one to the right (**dextro**), the other to the left (**laevo**). They therefore are said to be *optically active*.

**Polarized Light.** Light which has passed through a crystal of tourmaline or a Nicol prism (a specially constructed prism of Iceland Spar) is said to be **polarized**. Such light will pass through a second tourmaline crystal or Nicol prism only if it is held parallel to the first. This can be demonstrated by placing two clear tourmaline crystals one against the other and interposing them between a light and the eye. They will be transparent if their crystal axes are parallel; when one crystal is turned so that its axis is at right angles to that of the other, the intersection of the two crystals appears opaque (Fig. 22). If one of these crystals is now firmly set in an apparatus such as that indicated in Fig. 23

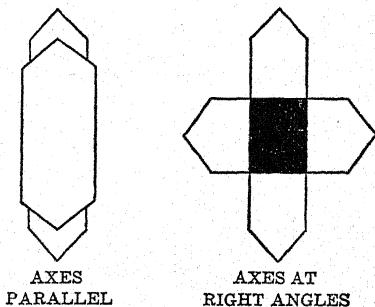


Fig. 22. Two tourmaline crystals crossed at right angles are opaque.

and the other placed at some distance from it on a movable axis, we have what is known as a **polariscope**. When nothing is interposed between the two crystals, the maximum amount of light can come through the apparatus and strike the eye of the observer only when the second crystal is exactly parallel to the first. If we now insert an optically active substance between the two crystals,

we find that we must turn the movable crystal to the right or left in order to get the greatest brightness. The direction and extent of this rotation depend on the nature of the substance and the amount of it through which the light passes. A number of organic liquids and solutions of solid compounds are optically active.

The physical explanation given for the phenomenon of optical activity is as follows: the light after passing through the first

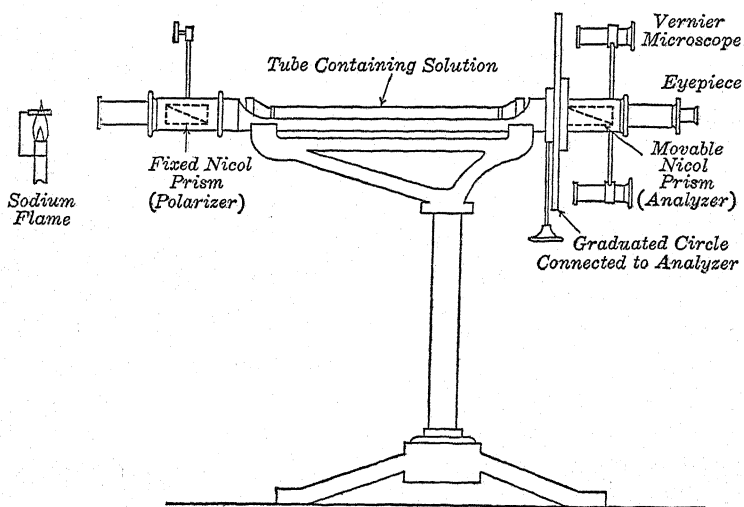


Fig. 23. Polariscope used in determining the optical activity of organic compounds. The solution of the compound is placed in the long glass tube which has parallel glass ends.

crystal is supposed to be vibrating in only one plane; therefore, the second crystal must be set in exactly the same plane in order to allow all the light to pass through it. Optically active substances have the power to rotate this plane of polarized light to the left or to the right

The optical activity of many solids is caused by the nature of the arrangement of the molecules in the crystal; however, this phenomenon does not concern the organic chemist. *The optical activity of organic compounds is a property of the molecule itself since it is manifested in the liquid state, in solution, and as a gas.*

It is important to have a standard method of comparing the optical activity of organic liquids. The *specific rotation* of a liquid is the angular rotation

(measured in a polariscope as explained above) produced by a column whose length is defined in terms of the specific gravity. Specific rotation is purposely so defined in order that *comparable weights* of material will be under observation each time. In the case of solutions, the concentration of the solution replaces the specific gravity. The two formulas for calculating the specific rotation  $[\alpha]$  from an observed rotation in the polariscope ( $\alpha_{\text{obs.}}$ ) are as follows:

$$\text{Liquids: } [\alpha] = \frac{\alpha_{\text{obs.}}}{l \times \text{sp. gr.}},$$

$$\text{Solutions: } [\alpha] = \frac{\alpha_{\text{obs.}}}{l \times c},$$

where  $l$  = length in decimeters of liquid or solution employed (usually 1 or 2 decimeters) and  $c$  is the weight of solute in 1 cc. The molecular rotation is usually defined as the specific rotation multiplied by the molecular weight and divided by a hundred.  $[M] = \frac{[\alpha] \times \text{M.W.}}{100}$ . Since specific rotation usually

varies with the wave length of light employed in making the measurement, it is common to denote this by a small letter or number. Thus,  $[\alpha]_D$  means the specific rotation measured with sodium light (D line of the spectrum), while such a symbol as  $[\alpha]_{5461}$  indicates that the wave length of light employed was 5461 Ångström units (Å). The specific rotation varies somewhat with the temperature and often greatly with the nature of the solvent.

**Pasteur's Separation of a Racemic Tartrate.** The first important advance in the understanding of optical activity was made by Pasteur<sup>1</sup> in 1848. At that time racemic tartaric acid, which is optically inactive, and the common dextro tartaric acid were both known. Pasteur was studying the crystal angles of the salts of the racemic acid. He noticed on examining certain very large crystals of the sodium ammonium salt that there seemed to be two different types of crystals which differed only slightly in the position of the crystal faces. These faces were arranged either in a left-handed fashion or in a right-handed fashion with regard to the crystal axis. Thus, one type of crystal could be considered the mirror image of the other, just as one's left hand is the mirror image of the right.

Pasteur laboriously separated these left-handed and right-handed crystals into two piles, dissolved them separately in water and examined the two solutions in the polariscope. To his delight he found that one solution turned the plane of polarized light to

<sup>1</sup> Pasteur's separation of racemic tartaric acid was accomplished at the beginning of his scientific career at the age of only twenty-six. He later studied fermentation and thus became interested in micro-organisms. This work led away from chemistry and towards medicine in which field he did the work with which his fame is popularly connected (see also p. 15).

the right, the other an equal amount to the left, — this in spite of the fact that the original salt had been entirely inactive! This classic experiment proved that in one instance, at least, the *inactive compound could be separated into two active forms*. It was evidently only a mixture of the well-known dextro acid and a new laevo form. The isomers were found to differ only in their effect on polarized light.

**The Problem of Optically Active Isomers.** Pasteur thus demonstrated that an optically inactive compound may be a mixture of equal amounts of two isomers, a **dextro compound** and a **laevo compound**. Such a **racemic mixture**, as it is called, may be separated as we have described. The great majority of inactive organic substances, however, are not racemic mixtures and can not be separated into active components. The problem of why only certain compounds have optically active isomers could not be answered in Pasteur's time. Only after the structural theory had been firmly established was it possible to connect the phenomenon of optical activity with the structure of the compounds. This van't Hoff and Le Bel did by means of their hypothesis in regard to the spatial arrangement of the atoms in a molecule.

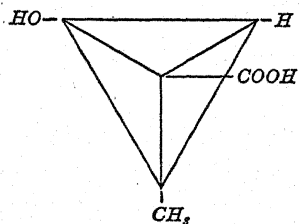
**The Tetrahedral Carbon Atom.** Le Bel and van't Hoff assumed that the valences of the carbon atoms were directed towards the corners of a more or less regular tetrahedron. To demonstrate this, they constructed solid models. These were not supposed to represent an actual picture of a carbon atom; they were only intended to show the spatial arrangement of the atoms in a molecule. The peculiar property of a tetrahedron is that *when four different things are attached to its corners, two arrangements are possible*. These differ as the *right hand differs from the left*; one arrangement is the mirror image of the other. If *two or more of the things attached to the four corners are the same, only one arrangement is possible*. This is a fact of geometry and in itself has nothing to do with chemistry; van't Hoff and Le Bel saw in it an explanation of optical activity and the peculiar examples of isomerism which had been noted in the case of the tartaric acids.

**Optically Active Isomers Are Stereoisomers.** If a tetrahedron with four different things attached can exist in two arrangements, so a carbon atom with four different atoms or groups arranged about it may exist in two forms. These two forms would be ex-

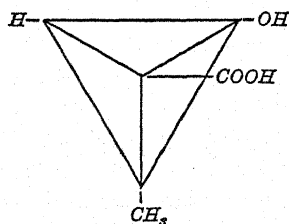
pected to differ in some right-handed or left-handed manner. This is exactly the case with optical isomers; the dextro and laevo forms are identical in all properties except their action on the plane of polarized light. According to this theory, therefore, optical isomers are stereoisomers and *differ only in the spatial arrangement of the atoms in the molecule.*

The fundamental postulate of the theory is that this isomerism is to be found only when the molecule can exist in two forms which are mirror images of each other. Such a molecule is said to be **asymmetric**. *Optical activity is a property of an asymmetric molecule.* In almost all cases an asymmetric molecule contains an atom with four different groups or atoms attached. Such an atom is called an *asymmetric atom*.

**Stereoisomers of Lactic Acid.** The simplest case to consider first is one in which there is only *one* asymmetric carbon atom. Lactic acid is such a case. The carbon atom starred in the formula is asymmetric:  $\text{CH}_3\text{CH}^*\text{OHCOOH}$ . Models of the two forms of lactic acid are shown below:



DEXTRO LACTIC ACID



[ LAEVO LACTIC ACID

There is no way of telling which of the above models correspond to the dextro acid and which to the laevo. It can only be said that if one is arbitrarily selected to correspond to the laevo form, the other must be the dextro. The racemic acid is a mixture of an equal number of the molecules of the dextro and laevo forms.

If possible, the student should handle actual solid models and convince himself of the fundamental geometrical fact which is the basis of stereoisomerism. The theory predicts a dextro lactic acid; a laevo lactic acid and a racemic mixture (inactive lactic acid). The experimental facts are in accord with this prediction. The acid which is prepared in the laboratory by synthetic methods (p. 228) is inactive; that formed by the fermentation of glucose

may be dextro, laevo or inactive according to the enzyme employed.

In the case of propionic acid,  $\text{CH}_3\text{CH}_2\text{COOH}$ , there is no asymmetric carbon atom in the molecule, and two different spatial arrangements are not possible. No stereoisomers are predicted, and none has ever been found. The theory of stereoisomerism has been drastically tested since it was first suggested. In every case, complete agreement has been found between the experimental facts and the predictions based on the theory.

**Racemic Mixtures and Racemic Compounds.** Two stereoisomers such as laevo and dextro lactic acid are sometimes spoken of as **enantiomorphs**. *They are identical in all physical and chemical properties except their action on polarized light.* The two isomers have the same rotating power, but turn the plane in opposite directions, one to the right and the other to the left. A mixture of two enantiomorphs may be merely a mechanical mixture of the two isomers, or it may be a loose molecular compound of the two. The first we speak of as a **racemic mixture**, the second, as a **racemic compound**. The racemic compound is met with when we are dealing with solids; it has physical properties different from those of the component isomers. In solution, it is usually largely dissociated and behaves much like a solution of a racemic mixture.

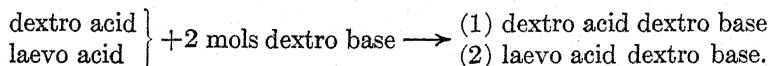
**Separation of Racemic Mixtures.** Since the two components of a racemic mixture have identical physical properties, they can not be separated by crystallization or by fractional distillation. This is unfortunate because, when we synthesize compounds in the laboratory by ordinary methods, we always obtain a racemic mixture. To obtain a variety of optically active products, it is, therefore, essential to have some method of separating a racemic mixture. Such a method is generally referred to as **resolution**.

The methods of separating racemic mixtures are as follows:

(1) If the compound forms crystals with two different arrangements of the faces, as in the case of the salts of tartaric acid, one may laboriously separate the crystals by hand. This method, for obvious reasons, is rarely employed.

(2) If the compound is fermented by bacteria or molds, usually one of the stereoisomers will be destroyed faster than the other. In this way, by the proper choice of bacteria it is often possible to prepare both forms from the inactive compound.

(3) The most general method is to combine the compound with some optically active substance. There are certain complex amines found in nature which are optically active; they are known as **alkaloids** (Chap. XXIX). These compounds form salts with acids. If the acid is a racemic mixture, there will be two sets of salts, corresponding to the two stereoisomers. These salts may be separated by fractional crystallization because they are not enantiomorphs and, therefore, differ in physical properties.<sup>1</sup> From them the pure dextro and laevo forms are obtained by treatment with acid, and the alkaloid is recovered. This method is summarized below:

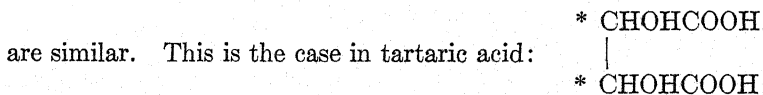


Two salts not enantiomorphs can be separated by crystallization.



In a similar manner optically active acids may be used to resolve racemic mixtures which contain a basic group, as in amines.

**Isomerism of Tartaric Acid.** When there are two or more asymmetric carbon atoms in the molecule, the situation is more complicated than in a simple case such as lactic acid. Let us first consider a compound where the two asymmetric carbon atoms



Since both asymmetric atoms have the same groups about them, they will affect the plane of polarized light to the same extent, but each may be either dextro rotatory or laevo rotatory.

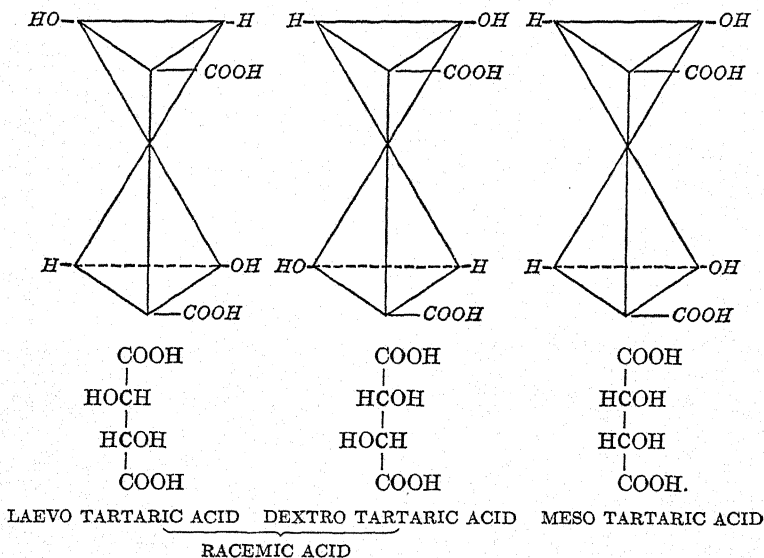
We are thus led to predict the following possible combinations:

- (1) both atoms dextro rotatory; (2) both atoms laevo rotatory;
- (3) one atom dextro, the other laevo. In the first two cases, the

<sup>1</sup> The fact that these two salts are not enantiomorphs and therefore differ in physical properties may be illustrated by a crude analogy. If we take a pair of gloves and tie to each glove a right-handed mitten we have a model of the *dextro* acid *dextro* base and *laevo* acid *dextro* base combination. We can readily convince ourselves that the two glove-mitten combinations are neither identical nor mirror images of each other.

effect of each atom reinforces that of the other. In the third case, they cancel each other, and, since the two atoms are *exactly opposite* in their effect on polarized light, the compound will be *optically inactive*. Such a compound is said to be *inactive by internal compensation*. It is not a racemic compound and obviously can not be separated into active forms; every molecule is exactly like every other molecule and each is inactive. **Mesotartaric acid** is the isomer which is inactive by internal compensation.

The following diagrams show the spatial arrangement of the groups in dextro tartaric acid, laevo tartaric acid and meso tartaric acid:

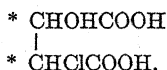


Racemic tartaric acid, as the name implies, is a racemic compound; in solution, it is a mixture of the dextro and laevo isomers. The solid is a molecular compound of one molecule each of the two forms.

**Plane Representation of Stereochemical Formulas.** Drawings of three-dimensional models such as those shown above or the models themselves are essential for the understanding of the subject of stereoisomerism. After the principles have been mastered, however, such methods of representing stereoisomers are cumbersome. A compact and convenient method of representing the

models consists in projecting them onto a plane. In the case of dibasic acids, it is agreed that the projection will be such that a carboxyl group is at the top and bottom of the plane diagram. This corresponds to a model in which the carboxyl groups are over each other as in the drawings. The plane diagrams are shown above under the drawings of the corresponding models.

**Compounds with Dissimilar Asymmetric Atoms.** The case of tartaric acid is peculiar in that the two asymmetric carbon atoms are alike. A more general case is illustrated by chloro-hydroxy-succinic acid:



In this compound the atoms attached to the two asymmetric carbon atoms are different (chlorine in place of hydroxyl). Therefore, each half of the molecule will rotate the plane of polarized light to a different extent. Since this is the case, there is no longer the possibility of a complete cancellation of the effect. Instead, we have *four* possible stereoisomers *all optically active*. They may be represented by the following symbols, where A represents the rotation caused by the asymmetric atom holding the OH group, and B that caused by the other. The signs + and - respectively refer to dextro and laevo rotation.



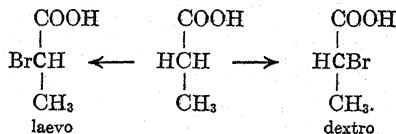
We have no way of telling whether A is greater or less than B, but it must be different since the atoms are dissimilar.

The four stereoisomers of chloro-hydroxy-succinic acid are the components of two racemic mixtures (or racemic compounds) as indicated above. These two different racemic mixtures differ in physical properties. The two known chloro-hydroxy-succinic acids are these two racemic mixtures; they melt at 145° and 154°. Both are inactive and both are separable. Stereoisomers which are not enantiomorphs are called **diastereoisomers**. Thus, 1 and 3, or 2 and 4 in the illustration above are diastereoisomers. Not being mirror images they differ not only in rotation but also in their physical properties. The problem of assigning the correct

spatial formula to each of the four active isomers is very difficult. Some of the methods used in such stereochemical investigations are considered in the last chapter of this book.

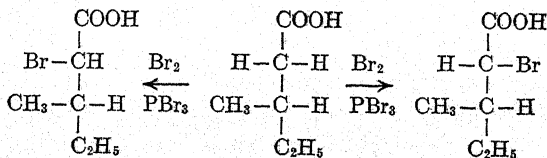
In general, it can be shown by studying models that in a compound with  $n$  asymmetric dissimilar carbon atoms there are  $2^n$  optically active isomers and  $\frac{2^n}{2}$  racemic mixtures. This rule does not apply to compounds, like tartaric acid, which contain similar asymmetric atoms.

**Synthetic Products.** Whenever a compound containing an asymmetric carbon atom is prepared in the laboratory, the racemic mixture (or compound) is the invariable product. Thus,  $\alpha$ -bromopropionic acid,  $\text{CH}_3\text{CHBrCOOH}$ , like lactic acid, exists in two active forms; yet when we prepare it by brominating propionic acid, the racemic mixture is always the result. In the production of an asymmetric atom — in this instance by the replacement of hydrogen by bromine — there is an even chance as to whether a right-handed or left-handed molecule will result.



On the average, an equal number of dextro and laevo molecules of bromo-propionic acid will be formed. The smallest amount of the product which we can examine in our polariscope contains many million molecules; even if there were one or two more dextro than laevo molecules in this sample, we could not detect their presence by our most delicate apparatus.

When a new asymmetric carbon atom is produced by synthetic means in a molecule already optically active because of an asymmetric atom, two optically active products may be obtained. Thus, the bromination of dextro  $\beta$ -methyl valeric acid yields two optically active products which are not mirror images of each other and, therefore, can be separated by the usual laboratory methods.



As in the case of propionic acid, bromine may replace the left or right handed hydrogen atom, but since the  $\beta$ -carbon atom is dextro and unaltered during the reaction, two substances  $++$  and  $+ -$  which are different are produced. Although in the case of propionic acid the left and right handed hydrogens are replaced in equal number, this is not so in the production of diastereoisomers. For some reason the presence of an asymmetric carbon atom in a molecule directs the formation of a second asymmetric carbon atom so that one diastereoisomeric form is produced in larger amounts than the other.

**Racemization.** Some optically active compounds lose their activity on heating or treating with certain reagents. This process, which may interfere with the transformation of one optically active substance into another active compound, is known as racemization. Many compounds are either racemized with great difficulty or not at all. When racemization occurs readily, it is usually possible to show that some special mechanism is involved in the transformation of the  $+$  to the  $-$  isomer and vice versa (see p. 616).

**Nature Produces Optically Active Compounds.** The chemical transformations which take place in living things almost always produce optically active materials. This is the most striking distinction between chemical reactions in the laboratory and in plants or animals. Practically all the natural products which contain an asymmetric carbon atom occur in an optically active form. The enzymes which are the natural catalysts can differentiate between a dextro and a laevo form; in their presence the odds are no longer even as to the formation of the one enantiomorph or the other. The second method given above of separating racemic mixtures illustrates this point.

Although all the physical and chemical properties of a pair of enantiomorphs are identical, their biochemical behavior is different. This is even true in the case of drugs which manifest their chemical action by some change in a large and complex organism. In most cases where both a dextro and laevo form of a drug have been prepared, the two have been found to differ markedly in their physiological action.

### QUESTIONS AND PROBLEMS

1. Discuss the isomerism of tartaric acid, naming all the isomers and stating the effect of each (in solution) on polarized light. (Draw diagrams representing the three-dimensional formulas.)

2. Indicate clearly the number of possible stereoisomers of each of the following compounds:  $\text{CH}_2\text{BrCH}_2\text{COOH}$ ,  $(\text{CH}_3)_2\text{CHCOCOOH}$ ,  $\text{CH}_3\text{CHOH-CHOHCH}_3$ ,  $\text{CH}_3\text{CHBrCOOH}$ ,  $\text{CH}_3\text{CHBrCHOHCOOH}$ ,  $\text{CH}_2\text{BrCHClCOOH}$ ,  $\text{CH}_2\text{OHCHOHCHOHCH}_2\text{OH}$ .

Indicate the effect of each isomer (in solution) on polarized light. Which of the inactive forms are inseparable?

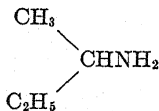
3. In which of the following cases could the optically inactive substance be separated into optically active isomers? Describe carefully three methods of accomplishing such a separation.

(a)  $(\text{CH}_3)_2\text{CHCOOH}$ ; (b)  $\text{CHOH}(\text{COOH})_2$ ; (c)  $(\text{CH}_3)_3\text{CCHOHCOOH}$ .

4. How many stereoisomers of propylene dibromide are possible? Which would you expect to obtain by the addition of bromine to propylene?

5. In what respects do enantiomorphs resemble each other? By what physical property may they be distinguished from each other? In what other respects do they differ?

6. Devise a method of separating the optically inactive amine



into the optically active isomers, making use of an optically active acid such as lactic acid.

7. In the bromination of inactive  $\beta$ -methyl valeric acid,  $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{COOH}$ , how many isomeric bromo acids would be expected?

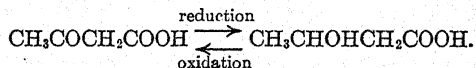
Would they be optically active? Why? Would you expect the isomers to be formed in equal amounts? Explain.

## CHAPTER XIII

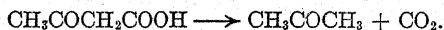
### ACETOACETIC ESTER AND MALONIC ESTER

Malonic ester and acetoacetic ester are two compounds of considerable practical importance and of great theoretical interest. They are very useful in the synthesis of acids, ketones and certain ring compounds. They have the peculiar property of forming salt-like metallic compounds under certain conditions, although they contain no free carboxyl group. The constitution of acetoacetic ester was a matter of vigorous controversy for many years. We shall consider acetoacetic ester first, since a study of this substance provides the clue to the salt-forming properties of malonic ester.

**Acetoacetic Ester and Acetoacetic Acid.** Acetoacetic ester is prepared from ethyl acetate by the action of sodium; this reaction will be described later. It is a mobile, colorless liquid with the molecular formula  $C_6H_{10}O_3$ . It is obviously an ester, as on careful hydrolysis with barium hydroxide the salt of acetoacetic acid is formed. This acid on reduction yields  $\beta$ -hydroxybutyric acid (p. 210) and from this compound acetoacetic acid is regenerated by cautious oxidation. This relationship makes it certain that acetoacetic acid has the formula,  $CH_3COCH_2COOH$ . It is a beta ketonic acid (classification, see p. 192). Its relationship to  $\beta$ -hydroxybutyric acid is obvious:



It very easily loses carbon dioxide on warming forming acetone:



In the urine of patients suffering from diabetes, both acetoacetic acid and  $\beta$ -hydroxybutyric acid are usually present in considerable amounts.

**The Peculiar Properties of Acetoacetic Ester.** From the structure of the acid, one would conclude that the ester had the formula,  $CH_3COCH_2COOC_2H_5$ . Indeed, many of its reactions are exactly those which would be predicted from this structure.

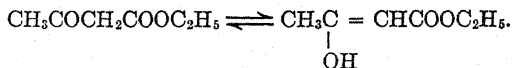
It is an ester, as has been noted; it is a ketone, as shown by its reactions with reagents which react with the carbonyl group. Peculiarly enough, it *also behaves like an hydroxyl compound*. When treated with metallic sodium it forms a metallic derivative with the evolution of hydrogen, and the same substance is formed by the action of sodium alcoholate ( $\text{NaOC}_2\text{H}_5$ ) or cold sodium hydroxide. This **sodium compound** we may represent for the present as  $[\text{CH}_3\text{COCHCOOC}_2\text{H}_5]\text{Na}$ , without committing ourselves as to the position of the metallic atom in the molecule. Acetoacetic ester also gives a deep color with ferric chloride. This reaction is similar to that of certain hydroxyl compounds called phenols which we shall meet later (p. 352). These facts and certain others led one group of chemists to contend that acetoacetic ester was in reality  $\text{CH}_3\text{C}=\text{CHCOOC}_2\text{H}_5$  and *not*



a ketonic ester. The sodium derivative, from this point of view, would be  $\text{CH}_3\text{C}(\text{ONa})=\text{CHCOOC}_2\text{H}_5$ . Others believed that the ketonic formula was correct and the sodium compound was  $\text{CH}_3\text{COCHNaCOOC}_2\text{H}_5$ .

**The Keto and Enol Forms.** The discussion of the structure of acetoacetic ester and certain similar compounds finally reached a point where it seemed as if one must say that this one compound behaved as though it had two different formulas, — one a ketonic formula, the other that of an unsaturated hydroxy compound. A reasonable explanation of this state of affairs would be the assumption that the liquid ester and its solutions were mixtures of two forms, the ketonic form,  $\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$ , and the hydroxy form,  $\text{CH}_3\text{C}(\text{OH})=\text{CHCOOC}_2\text{H}_5$ . This, indeed, turned out to be the case. By cooling the ester to a low temperature, a crystalline solid was obtained which gave no color with ferric chloride and failed to show the other peculiar reactions which indicated an unsaturated hydroxyl compound. By acidification of the sodium compound  $[\text{CH}_3\text{COCHCOOC}_2\text{H}_5]\text{Na}$  at  $-78^\circ$ , an oil was obtained which showed the peculiar reactions of acetoacetic ester in a marked degree. This oil is undoubtedly the unsaturated hydroxy compound; the crystalline solid is the ketonic ester. On allowing either the solid or the liquid to stand at room temperature for some time, a liquid acetoacetic ester was formed identical in all respects to the usual compound.

The isolation of the two forms of acetoacetic ester ended the controversy. The liquid which behaved like two substances was in reality a *mixture of the keto form and the hydroxy compound*. The latter came to be known as the **enol form**. The two are in a reversible equilibrium,



The conversion of one form into the other is rapid but not instantaneous. The enol form has the salt-forming properties. If the equilibrium mixture (the ordinary liquid ester) is treated with sodium alcoholate, the enol form reacts:

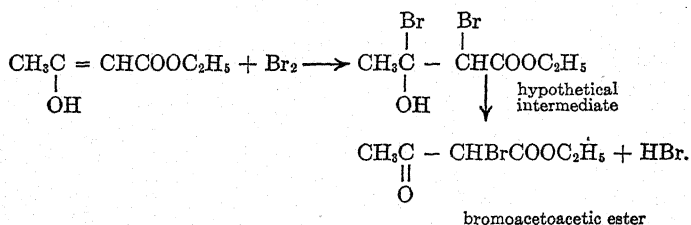


As this is removed from the equilibrium, the keto form changes over to the enol which, in turn, is neutralized by the sodium alcoholate. Thus, eventually all the material is converted into the sodium compound.

**Tautomeric Equilibria.** The change of one form of acetoacetic ester into the other is spoken of as a **tautomeric change**. It will be noted that only the shift of a hydrogen atom and a double linkage is involved. The hydrogen atom in this particular system is mobile and can change places easily. The rate at which the one form shifts into the other is catalyzed by traces of alkali. Even soft glass has sufficient alkali in it to promote the reaction. Quartz, however, does not. Therefore, if the liquid equilibrium mixture is carefully distilled in a quartz apparatus, it can be separated into the two forms. The enol form is slightly more volatile and distills first; the pure keto form is left behind. On standing, each slowly changes into the same equilibrium mixture.

**Methods of Determining Enol Content.** The early attempts to measure the amount of enol or keto form in the liquid failed because the reagents employed reacted too slowly. The one form had sufficient time to shift into the other before the reaction was complete. For this reason, as we have seen, the equilibrium mixture behaves towards ketonic reagents as though it were all keto and towards reagents for the enol form as though it were all enol.

The analytical method commonly used is that devised by Kurt H. Meyer. It is based on the fact that the reaction between bromine and the enol form is extremely rapid. It consists in rapidly titrating a weighed sample with an alcoholic solution of bromine, keeping the temperature at 0° to decrease the rate of rearrangement. The first slight excess of bromine is the end point which must be taken. (This excess soon disappears and eventually one molecule of bromine per mole of compound would be consumed if the titration were continued, because of the continual shift of the keto to enol form.) The reaction is:



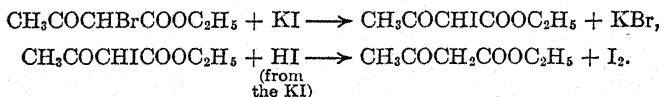
The keto form does not react with the bromine in the short time required for the titration.

It has been found by the bromine titration that the liquid equilibrium mixture of acetoacetic ester contains 92.6 per cent of keto form and only 7.4 of the enol. In a solution, the composition of the equilibrium mixture depends on the nature of the solvent. For example, in water there is only 0.4 per cent enol, while in hexane there is 46 per cent.

The simple rapid titration with bromine outlined above is called the direct method. It is the best method for determining the enol content of most derivatives of acetoacetic ester. In the case of acetoacetic ester itself, it gives values that are somewhat erratic and too high because the equilibrium shifts somewhat even under these conditions. The *indirect method*, also devised by Meyer, is, therefore, used in this and a few similar cases. This consists in adding as rapidly as possible (in a few seconds) an excess of bromine, then *at once* an excess of a compound which will destroy all free bromine (this is beta naphthol). The result is that an excess of free bromine is present for only a few seconds, and in this time the shift of the equilibrium is probably not serious.

All the enol form has been converted into a bromo compound by this short exposure to bromine. The amount of this bromo compound (and hence the amount of enol) is determined by adding potassium iodide solution. The bromo compound liberates iodine and is itself reduced. The iodine can be titrated with standard thiosulfate in the usual way. (There is no need

for haste after the excess of bromine has been destroyed.) The equations are:

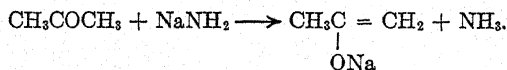


**Enolic Forms of Other Compounds.** All beta ketonic esters with the general formula  $\text{RCOCH}_2\text{COOR}'$  exist in a keto and an enol form, but the two pure forms have been isolated in only a few cases. The beta diketones with the general formula  $\text{RCOCH}_2\text{COR}'$  likewise have an enol form  $\text{RC} = \text{CHCOR}'$ , and

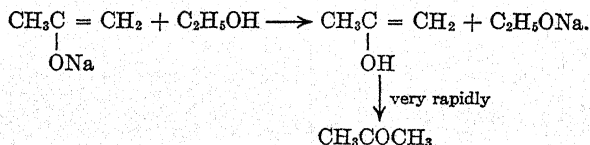


a keto form  $\text{RCOCH}_2\text{COR}'$ ; the liquid substance is an equilibrium mixture. When such compounds are solid at room temperature (by virtue of groups of high molecular weight in the molecule), it is often possible to isolate two crystalline, isomeric compounds — one a keto form, the other an enol. In solution, or in the molten state, an equilibrium is reached.

Undoubtedly an enolic form of even the simple aldehydes and ketones can have a transient existence and may even exist in very small quantities in equilibrium with the usual ketonic form. The metallic salts of such enolic forms of the simple ketones can be prepared (in the absence of water or alcohol) by a number of methods. For example, the ketone (in ether solution) may be heated with sodamide. The following equation illustrates such a reaction with acetone:



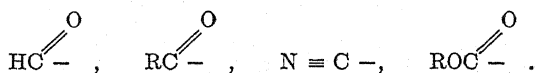
These metallic derivatives of the simple ketones are decomposed by water, acid, or even alcohol, regenerating the ketone. All attempts have so far failed to obtain evidence of the existence of the enol form which is presumably the first product; it must shift into the ketonic form very rapidly.



# SUMMARY OF ENOLIZATION OF SIMPLE CARBONYL COMPOUNDS

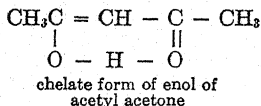
NAME	ENOL FORM	KETO FORM	PER CENT ENOL AT EQUILIBRIUM IN DILUTE SOLUTION
Beta ketonic aldehydes	$\text{RCOH} = \text{CHOH}$	$\text{RCOCH}_2\text{CHO}$	greater than 98 per cent
Acetylacetone (1, 3 diketone)	$\text{CH}_3\text{COCH} = \text{CCH}_3$   OH	$\text{CH}_3\text{COCH}_2\text{COCH}_3$	83 per cent
Methylacetylacetone	$\text{CH}_3\text{COC} = \text{CCH}_3$   CH <sub>3</sub> OH	$\text{CH}_3\text{COCHCOCH}_3$   CH <sub>3</sub>	31 per cent
Acetoacetic ester	$\text{CH}_3\text{C} = \text{CHCOOC}_2\text{H}_5$   OH	$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	10 per cent
Methylacetoacetic ester	$\text{CH}_3\text{C} = \text{CCOOC}_2\text{H}_5$   OH CH <sub>3</sub>	$\text{CH}_3\text{COCHCOOC}_2\text{H}_5$   CH <sub>3</sub>	4 per cent
Malonic ester	$\text{C}_2\text{H}_5\text{OC} = \text{CHCOOC}_2\text{H}_5$   OH	$\text{C}_2\text{H}_5\text{OCOCH}_2\text{COOC}_2\text{H}_5$	less than 0.01 per cent
Simple ketones and aldehydes	$\text{RC} = \text{CHR}$   OH	$\text{RCOCH}_2\text{R}$	less than 0.01 per cent (probably much less)

The table (p. 236) gives the percentage of enol in equilibrium with the keto form at room temperature for a number of substances. (All compounds are compared in dilute alcoholic solution.) It is evident that the beta diketones and beta ketonic esters occupy an intermediate position between the  $\beta$  ketonic aldehydes, which are practically entirely enolic, and the simple ketones, which are almost entirely ketonic. In general, it is found that enolization is increased by the presence of the following unsaturated groups (often called negative groups) attached to the alpha carbon atom (*i.e.*, in the beta position to the carbonyl group):



*These same groups in any other position in the molecule are without effect.* For example,  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$  shows none of the peculiar properties of acetoacetic ester, but is like acetone.

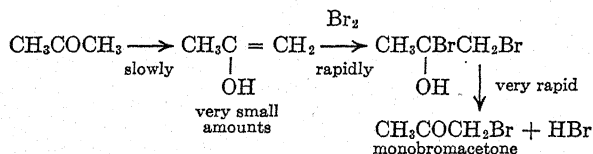
**Chelation.** On distillation of an equilibrium mixture of acetoacetic ester in a quartz apparatus, the enol form distills first. This is unexpected. One would predict that the enol form should be less volatile than the keto form since alcohols boil at higher temperatures than the corresponding ketones (*e.g.*, isopropyl alcohol at  $82^\circ$ , acetone at  $56^\circ$ ). In the case of a number of tautomeric enolic compounds which contain the grouping  $-\text{COCH}=\text{C}(\text{OH})-$ , it has been found that the enolic form is more volatile than the ketonic. Furthermore other physical properties of the enol indicate that in some way the hydroxyl group is masked. This is probably due to the formation of a peculiar sort of ring in which a hydrogen atom has a covalency of two. Certain metallic derivatives of enols, particularly the beryllium and copper compounds, contain such rings which are called **chelate rings**. The formation of such rings is known as **chelation**.



The chelate ring is very stable in the case of certain metallic derivatives; the metal atom holds both oxygen atoms in proper coördination positions by usual covalent links. The divalent hydrogen bond, however, is weak (it is involved in the association to double molecules of such hydroxyl compounds as acids and

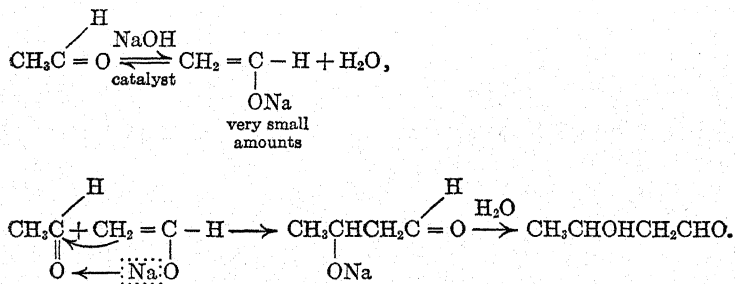
some alcohols). The chelate form is thus probably in mobile equilibrium with a small amount of the true hydroxy compound which is responsible for the reactions of the enol.

**Enolization as an Explanation of Certain Reactions.** Attention has been repeatedly called to certain peculiarities of the alpha hydrogen, in aldehydes, ketones, acid chlorides, and esters. For example, it is this hydrogen atom which is so relatively easily replaced by halogen (pp. 100 and 124) and which is involved in certain condensation reactions (p. 118). It seems very probable that these peculiarities are due to the fact that the hydrogen in the alpha position can enolize, and that the enolic form is involved in the reaction. For example, the bromination of acetone probably proceeds through the following steps:

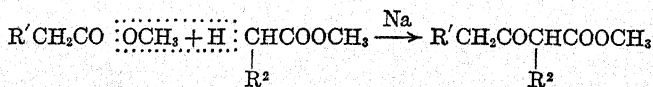


Similar reactions may be written for other halogenations involving a hydrogen on a carbon atom alpha to a carbonyl group.

In the aldol condensation and many similar processes, a small amount of enol may be the actual reactant. For example, the following mechanism has been suggested for the formation of aldol (p. 118):



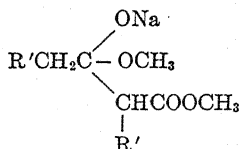
**Ester Condensations.** The preparation of acetoacetic ester illustrates a general reaction of esters which contain the  $-\text{CH}_2\text{COOR}$  grouping. The condensing agents most frequently used in this reaction are metallic sodium and sodium ethoxide. The ester condensation constitutes a general method of preparing  $\beta$ -ketonic esters:



$\text{R}'$  and  $\text{R}^2$  may be the same or different. Needless to say, when

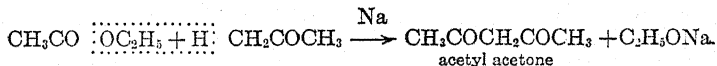
$R'$  and  $R^2$  are different a complex mixture is obtained which in many cases is very difficult to separate.

It should be noticed that this reaction is connected with the enhanced reactivity of the alpha carbon atom (p. 238). It is probable that the first step is the formation of a sodium compound of the enolate of the ester; this adds to the carbonyl group of a second molecule of ester. The resulting complex



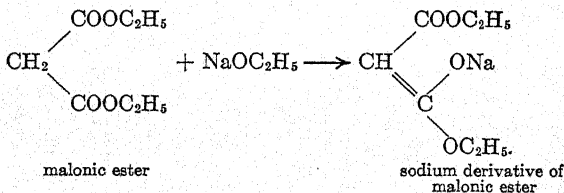
loses the elements of sodium methylate to give the corresponding ketonic ester.

Esters will also condense with many ketones to form  $\beta$ -diketones, the alpha hydrogen atom being involved:



**Malonic Ester.** Ethyl malonate or malonic ester,  $CH_2(COOC_2H_5)_2$ , occupies a position intermediate between acetoacetic ester and a simple ketone like acetone. The equilibrium mixture contains too little enolic form to be detected; indeed the enol form has never been isolated. However, clear evidence for the existence of such a form may be obtained. If the sodium compound,  $C_2H_5OOCCH = C(ONa)OC_2H_5$ , is acidified at a low temperature, an oil is produced which contains a large amount of the enol form as determined by Meyer's method. This oil rapidly reverts to the ordinary malonic ester in which no enolic form can be found.

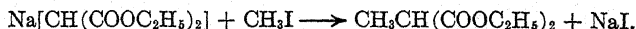
Malonic ester differs from acetone in that the sodium derivative of the enol form is stable in alcohol solutions. This fact has enormous practical consequences, since it enables us to prepare **sodium malonic ester** by the action of sodium alcoholate on the ester itself. As we shall see in the next paragraphs, this sodium derivative, like that of acetoacetic ester, is of great value in synthesis:



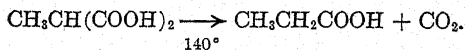
The ethyl ester of malonic acid is almost always the ester employed in the laboratory though the methyl ester will serve equally well. Ethyl malonate (malonic ester) is a liquid boiling at 198°. It is formed by esterifying malonic acid in the usual way or directly from the half nitrile of malonic acid (cyanoacetic acid) by the direct action of alcohol and acid (p. 200). On hydrolysis ethyl malonate yields malonic acid. It should be noted that there is no evidence of the formation of any enolic form of *malonic acid* itself. It is also important to distinguish clearly between the sodium derivative of malonic ester (also called the sodium salt of malonic ester) and the usual salts of malonic acid, such as  $\text{CH}_2(\text{COONa})_2$ , disodium malonate. *Malonic ester resembles acetoacetic ester in that it readily forms a sodium salt but differs from acetoacetic ester in that the pure liquid contains no appreciable quantity of an enolic form.*

#### USE OF MALONIC ESTER IN SYNTHESIS

**Alkylation of Malonic Ester.** The sodium compound of malonic ester reacts rapidly with alkyl halides, forming compounds in which the alkyl group is attached to the central carbon atom. In writing equations for such reactions, it is simplest to use the noncommittal formula for the sodium compound,



The fact that the methyl group is found linked to *carbon instead of oxygen* is surprising. In a sense it constitutes an exception to the general rule in organic reactions that in a replacement reaction the entering atom or group takes the place of the atom which is removed. There can be no doubt of the facts, however, as the product on hydrolysis yields a dibasic acid,  $\text{CH}_3\text{CH}(\text{COOH})_2$ . This on heating loses carbon dioxide and forms propionic acid,

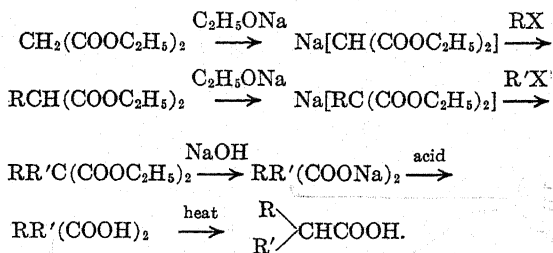


It will be recalled that malonic acid loses carbon dioxide when heated, and the alkyl derivatives have the same property.

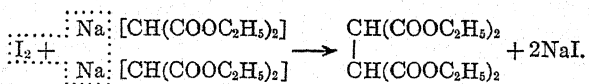
There is no agreement among chemists as to why the alkylation of sodium malonic ester produces a compound with the alkyl group on carbon. This is an interesting problem but its discussion is outside the scope of this book.

The combination of the two reactions just mentioned is very valuable in the synthesis of acids. In the example above, propionic acid was synthesized. If ethyl iodide is used in place of the methyl compound, the final product is butyric acid. Any simple alkyl halide can be used in this reaction. Secondary halides react with difficulty, and tertiary halides can not be employed.

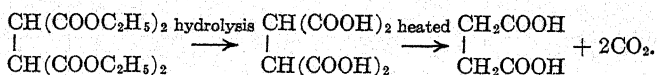
**Synthesis of Forked Chain Acids.** In addition to its use in preparing straight chain acids, malonic ester can be used in preparing acids with a branch in the chain next to the carboxyl group. This is possible because the monoalkyl malonic esters,  $RCH(COOC_2H_5)_2$ , also form sodium salts, which in turn will react with alkyl halides. Using  $RX$  and  $R'X$  to indicate two alkyl halides (with the same or different alkyl groups), we may outline the steps in this synthesis as follows:



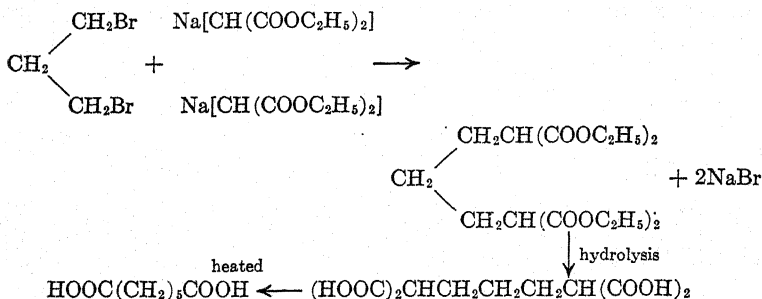
**Synthesis of Dibasic Acids.** Malonic ester may be used very advantageously in the synthesis of dibasic acids. The simplest illustration is the preparation of succinic acid. The essential reaction here is between iodine and sodium malonic ester. The iodine combines with the sodium, and two malonic ester residues join together at the central carbon atoms. The reaction is as follows:



The tetraester thus produced is readily converted to succinic acid by hydrolysis and removing the two extra carboxyl groups (as carbon dioxide) by heating:



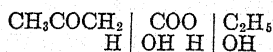
A different reaction is involved in the synthesis of acids of the type  $\text{HOOC}(\text{CH}_2)_n\text{COOH}$ . Here we may start with a dihalide,  $\text{CH}_2\text{Br}(\text{CH}_2)_x\text{CH}_2\text{Br}$ , having four less carbon atoms than the desired acid. Both ends of the chain react in a normal way as the following reaction with trimethylene bromide illustrates:



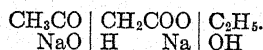
#### USES OF ACETOACETIC ESTER IN SYNTHESIS

The use of acetoacetic ester in synthetical work depends largely on two types of decomposition which acetoacetic ester and its alkyl derivatives undergo when treated with alkali. If a *dilute* alkaline solution is employed, the ester group is first hydrolyzed and the resulting sodium salt of acetoacetic acid (or substituted acetoacetic acid) loses carbon dioxide when the solution is acidified. Inorganic acids may be used in place of dilute alkali for this hydrolysis. In both cases a ketone is formed. If *concentrated* sodium hydroxide is employed, however, the molecule cleaves in such a way as to produce the sodium salts of two acids. These two methods of decomposition are illustrated by the following diagrams:

"Ketonic cleavage" with  
*dilute* NaOH or acids

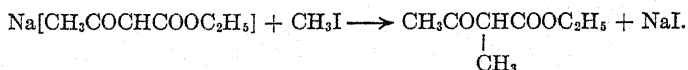


"Acid cleavage" with *con-*  
*centrated* NaOH

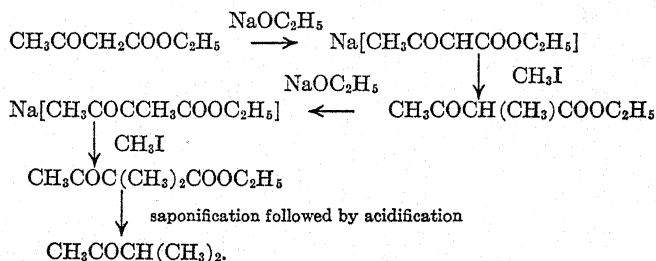
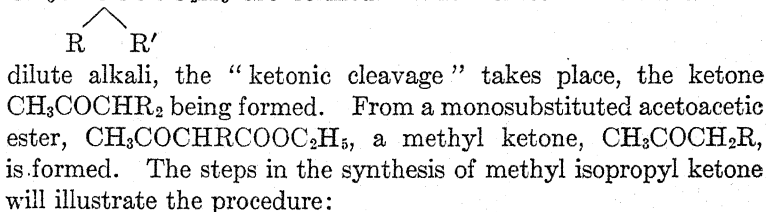


The "ketonic cleavage" is taken advantage of in the synthesis of ketones. The "acid cleavage" may be used for the preparation of substituted acids. Thus, the cleavage of  $\text{CH}_3\text{COCR}_2\text{COOC}_2\text{H}_5$  would yield the acid  $\text{R}_2\text{CHCOOH}$ . This method of synthesizing acids is now less used than the method which employs malonic ester.

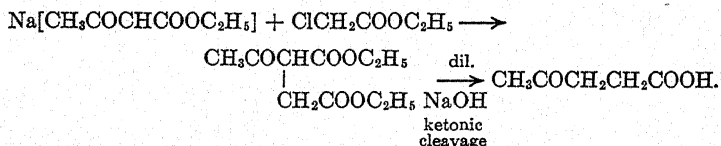
**Acetoacetic Ester Synthesis of Ketones.** The alkylation of the sodium salt of acetoacetic ester proceeds in the same manner as in the case of malonic ester:



The process can be repeated, also, and compounds of the type  $\text{CH}_3\text{COCCOOC}_2\text{H}_5$  are formed. When these are treated with

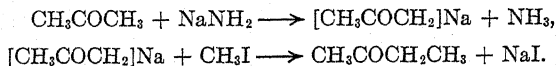


**Certain Other Uses of Acetoacetic Ester.** A great variety of compounds containing the grouping  $\text{CH}_3\text{COCH}$  may be prepared from acetoacetic ester. The synthesis of laevulinic acid,  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$ , will serve as one illustration. The reactions are:



**Direct Alkylation of Ketones.** In some cases the direct alkylation of ketones may be accomplished. It has already been stated that acetone and other simple ketones will react with sodamide ( $\text{NaNH}_2$ ) in dry ether to form a metallic derivative. These compounds can be alkylated, and just as in the case of acetoacetic ester or malonic ester, the *alkyl group becomes attached to carbon*.

The direct alkylation of acetone by this procedure with methyl iodide yields first methyl ethyl ketone,  $\text{CH}_3\text{COCH}_2\text{CH}_3$ :



On treatment again with sodamide and then a further amount of methyl iodide, a mixture of two ketones is produced:  $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3$  and  $\text{CH}_3\text{COCH}(\text{CH}_3)_2$ . In this way the process may be repeated until hexamethyl acetone,  $(\text{CH}_3)_6\text{CCOC}(\text{CH}_3)_6$ , is formed. This interesting substance has already been referred to as showing almost none of the typical reactions of a ketone (p. 144).

### QUESTIONS AND PROBLEMS

1. Outline the steps in the synthesis of the following acids with the aid of malonic ester:  $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ ,  $(\text{CH}_3)_2\text{CHCOOH}$ ,  $(\text{CH}_3)_2\text{CHCH}_2\text{COOH}$ ,  $\text{CH}_3\text{CH}_2\text{CHCOOH}$ .



2. Illustrate the use of acetoacetic ester in the synthesis of ketones by outlining the steps in the preparation of the following compounds:  $\text{CH}_3\text{COCH}_2\text{CH}_3$ ,  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_3\text{COCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ,  $(\text{CH}_3\text{CH}_2)_2\text{CHCOCH}_3$ .

3. Compare and contrast the isomerism of the following pairs of compounds: ethyl alcohol, methyl ether; *n*-propyl alcohol, isopropyl alcohol; racemic tartaric acid, meso tartaric acid; dextro lactic acid, laevo lactic acid; enol form of acetoacetic ester, keto form of acetoacetic ester.

4. In what respects would you expect the following compounds to resemble each other? In what respects might they differ?  $\text{CH}_3\text{CH}(\text{COOC}_2\text{H}_5)_2$ ,  $\text{CH}_3\text{CH}_2\text{COCH}_2\text{COOCH}_3$ ,  $\text{CH}_3\text{COCH}_2\text{CHO}$ ,  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COCH}_3$ .

5. Outline the evidence which indicates that liquid acetoacetic ester is an equilibrium mixture of a keto and enol form.

6. If  $\beta$ -hydroxybutyric acid were oxidized in a boiling solution what product would you expect to be formed?

7. Starting with acetic acid, methyl and ethyl alcohols show how one could synthesize the following:  $(\text{CH}_3\text{CH}_2)_2\text{CHCOOH}$ ,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_3$ ,  $(\text{CH}_3)_2\text{CHCOH}(\text{CH}_3)_2$ ,  $\text{CH}_3\text{CH}_2\text{CHCHBrCH}_3$ ,  $\text{CH}_3\text{CH}(\text{COOH})\text{CH}(\text{CH}_3)-$



$\text{COOH}$ ,  $\text{CH}_3\text{COCH}(\text{CH}_3)\text{CH}_2\text{COOH}$ . (Employ the acetoacetic ester synthesis, or the malonic ester synthesis where possible.)

8. Predict the action of sodium ethylate on the following (give reasons for your prediction): (a)  $\text{CH}_3\text{COCH}_2\text{CHO}$ ; (b)  $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_2\text{COCH}_3$ ; (c)  $\text{CH}_3\text{CH}_2\text{COCH}_3$ ; (d)  $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CN}$ ; (e)  $\text{C}_2\text{H}_5\text{CH}(\text{COOC}_2\text{H}_5)_2$ .

9. Outline a mechanism involving enolization for each of the following reactions: (a) bromination of an ester; (b) the action of sodamide on methylacetone; (c) acetylacetone treated with ethyl magnesium bromide (ethane formed).

10. Illustrate with equations Kurt Meyer's method for determining enolic content. How would you explain the fact that acetoacetic ester in hexane is enolized to the extent of 46 per cent whereas in water the enol content is 0.4 per cent?

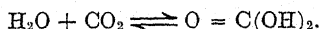
11. Define: (a) tautomeric change; (b) acid and ketonic cleavage of acetoacetic ester; (c) direct alkylation of ketones; (d) chelation.

12. Differentiate by simple tests between: (a)  $\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$  and  $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOCH}_3$ ; (b)  $\text{CH}_2(\text{COOC}_2\text{H}_5)_2$  and  $(\text{CH}_3)_2\text{C}(\text{COOC}_2\text{H}_5)_2$ ; (c)  $\text{CH}_3\text{COCH}_2\text{COOH}$  and  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$ ; (d)  $\text{CH}_3\text{COCHBrCOOC}_2\text{H}_5$  and  $\text{CH}_3\text{CHBrCH}_2\text{COOC}_2\text{H}_5$ .

## CHAPTER XIV

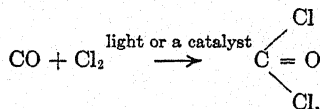
### DERIVATIVES OF CARBONIC ACID

Carbonic acid, ( $\text{H}_2\text{CO}_3$ ), is a dibasic acid which occupies an exceptional position because it does not contain two carboxyl groups. The free acid is not known in the pure state; an aqueous solution of carbon dioxide undoubtedly contains a considerable proportion of carbonic acid in equilibrium with the gas



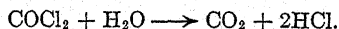
The salts of carbonic acid, the carbonates, can be prepared by adding alkali to such aqueous solutions. They are considered fully in books dealing with inorganic chemistry and for this reason need not be further discussed. The derivatives of carbonic acid which are of interest to the organic chemist are usually prepared neither from carbon dioxide nor the carbonates. The acid chloride of carbonic acid,  $\text{COCl}_2$ , known as phosgene, is the more usual starting point.

**Phosgene.** Phosgene is prepared by the action of carbon monoxide and chlorine in the presence of light or a catalyst:

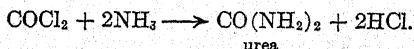


Phosgene is also formed by the oxidation of chloroform or carbon tetrachloride. The slow oxidation of chloroform by air has already been mentioned (p. 133).

The two chlorine atoms in phosgene are directly attached to the carbon atom of a carbonyl group. For this reason the reactions of the substance are those of an acid chloride. When treated with water, carbon dioxide and hydrochloric acid are formed:

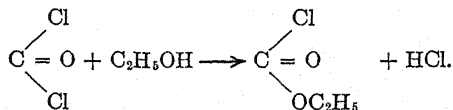


With ammonia the diamide is formed. It is known as **urea**:



When alcohol and phosgene interact the reaction proceeds in

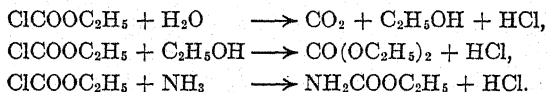
two definite steps; the product of the first step may be isolated before it reacts further. It is known as **ethyl chlorocarbonate**:



Phosgene is a gas at ordinary temperatures (boiling point  $8^\circ$ ). It has a very irritating odor, and is extremely poisonous. It was largely used as a war gas in the World War. Experiments have shown that a concentration of less than a milligram per liter will kill animals after a short exposure.

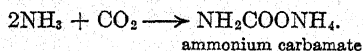
**Ethyl Chlorocarbonate.** Ethyl chlorocarbonate,  $\text{ClCOOC}_2\text{H}_5$ , is prepared from phosgene and ethyl alcohol as just described. It is a liquid insoluble in water, with an unpleasant sharp odor, and boils at  $93^\circ$ . It is also known as **chloroformic ester**, since it may be regarded as the ester of a formic acid in which the hydrogen has been replaced by a chlorine atom. Chloroformic acid itself,  $\text{ClCOOH}$ , should be the first product formed by the hydrolysis of phosgene, but it has never been isolated. It probably decomposes at once into hydrochloric acid and carbon dioxide.

Ethyl chlorocarbonate is both an acid chloride and an ester. Many of its reactions are those characteristic of an acyl halide. Hydrolysis, alcoholysis, and ammonolysis all proceed readily:

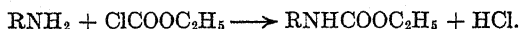


The product of the second reaction written above is the diethyl ester of carbonic acid, **ethyl carbonate**. It is the final product of the interaction of phosgene and alcohol. It is a sweet smelling liquid insoluble in water and boiling at  $126^\circ$ . It is easily hydrolyzed and yields carbon dioxide and alcohol.

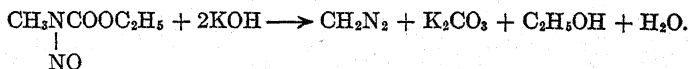
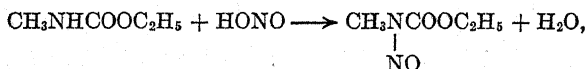
**Urethanes or Esters of Carbamic Acid.** The product of the interaction of ammonia and chlorocarbonate is an ester of carbamic acid, also known as a **urethane**,  $\text{NH}_2\text{COOR}$ . **Carbamic acid** itself,  $\text{NH}_2\text{COOH}$ , is unknown in the free state, but its salts are stable compounds. The simplest of these is the ammonium salt which is formed by the direct union of dry carbon dioxide and dry ammonia:



The ethyl ester of carbamic acid (ethyl urethane) is a crystalline solid melting at  $150^{\circ}$  and boiling at  $184^{\circ}$ . It has no basic properties. It has a strong hypnotic effect on animals and is often used in physiological experiments. Some of the urethanes of the higher alcohols have been marketed as hypnotics and sedatives. When chlorocarbonic ester reacts with a primary or secondary amine instead of ammonia an **alkyl urethane** results:



**Diazomethane.** The very interesting and useful substance diazomethane,  $\text{CH}_2\text{N}_2$ , can be prepared from an alkyl urethane. If the urethane obtained from methylamine and chlorocarbonic ester is treated with nitrous acid, the hydrogen on the nitrogen is replaced by a nitroso group; this is similar to the reaction of secondary amines (p. 160). When this nitroso compound is treated with strong alkali, diazomethane is formed:



Diazomethane is a yellow gas which liquefies at  $-23^{\circ}$  and is very soluble in ether. It reacts with organic acids with the elimination of nitrogen and formation of a methyl ester according to the following equation:



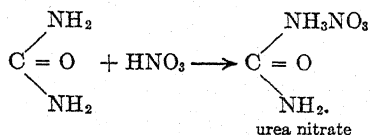
It is often used in ether solution for the preparation of methyl esters. It is slowly decomposed by water, particularly in the presence of mineral acids, forming methyl alcohol and nitrogen. It is an extremely poisonous substance and attacks the skin, lungs, and eyes.

Two formulas for diazomethane are often written  $\text{CH}_2 \begin{smallmatrix} \text{N} \\ \parallel \\ \text{N} \end{smallmatrix}$  and  $\text{CH}_2 = \overset{+}{\text{N}} = \overset{-}{\text{N}}$ . The evidence from physical measurements favors the latter.

## UREA

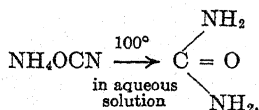
Urea, or carbamide,  $\text{CO}(\text{NH}_2)_2$ , because of its significance in physiological chemistry, is an important derivative of ammonia. It is the principal end-product of the metabolism of nitrogenous foods in the body and is excreted in the urine.

Urea is the diamide of carbonic acid but, unlike other amides, it has basic properties and forms salts. Both urea and its salts are white crystalline solids soluble in water. Urea itself melts at  $132^\circ$  and decomposes on further heating. In the isolation of urea from urine, the concentrated solution is treated with nitric acid; on cooling, urea nitrate crystallizes from the mixture:



Urea is a very weak base (see Fig. 20, p. 158) and its salts are largely hydrolyzed in aqueous solution.

**Wöhler's Synthesis of Urea.** The first synthesis of urea was accomplished by Wöhler<sup>1</sup> in 1828. He found that, on slow evaporation, a water solution of ammonium cyanate yielded urea:

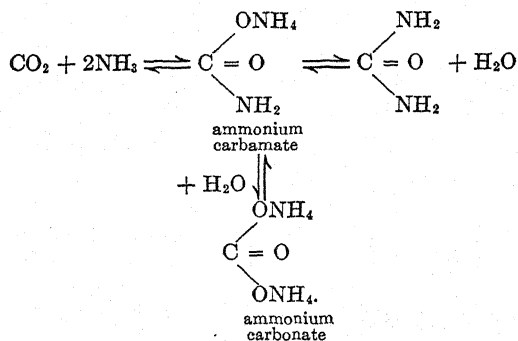


His discovery awakened great interest. It was the first synthesis of a typical natural product, and did much to break the barrier surrounding the supposedly mysterious chemistry of living things. The preparation of urea from phosgene (p. 246) was accomplished later.

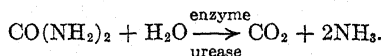
**Industrial Preparation of Urea.** Urea is now prepared on a large scale industrially for use as a special (and expensive) fertilizer and for the production of certain resins. The reaction employed is similar to one of the general methods of preparing amides; namely, — the heating of an ammonium salt. Carbon dioxide and ammonia are heated under pressure. The exact control of the temperature and pressure is important because a series of

<sup>1</sup> Friedrich Wöhler (1800–1882), Professor at the University of Göttingen, Germany.

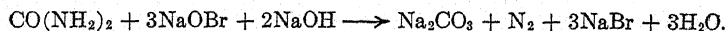
reversible reactions is involved; a good yield of urea is only obtained under special conditions.



**Reactions of Urea.** The hydrolysis of urea in water solution is brought about in the presence of the enzyme *urease*, which has been isolated from the soy bean. This method forms the basis of a clinical method of determining urea. The amount of ammonia formed from a known weight of sample can be easily determined colorimetrically, or by titration with a standard acid:

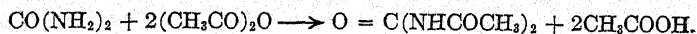


The reaction with sodium hypobromite (in a sense, the *Hofmann* reaction) has also been used for the determination of the amount of urea in urine. The volume of nitrogen evolved from a known sample can easily be measured in a suitable apparatus:

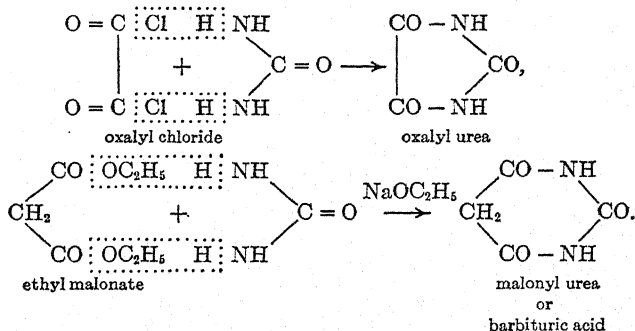


As so often happens in organic chemistry, the reaction does not proceed entirely in the way outlined by the above equation. The method must be standardized by finding the amount of nitrogen evolved under certain conditions with known weights of urea.

**The Ureides.** The hydrogen atoms of urea may be replaced by acyl groups by the action of an acid anhydride on urea. In this way *monoacetyl urea*,  $\text{NH}_2\text{CONHCOCH}_3$ , and *diacetyl urea*,  $\text{CH}_3\text{CONHCONHCOCH}_3$ , can be prepared. These substances, which may be defined as the acyl derivatives of urea, are known as *ureides*:



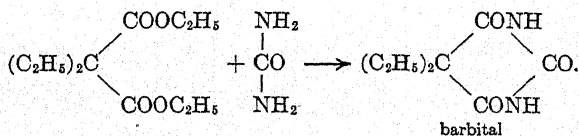
The most important ureides are the **cyclic ureides**, derived from the dibasic acids, oxalic acid and malonic acid. These compounds are conveniently formed by treating urea with the acid chloride or the diethyl ester of the dibasic acid. In the latter case sodium ethylate is used as a catalyst for the reaction:



The second reaction above is reminiscent on the one hand of the formation of amides from esters (p. 149) and on the other of the condensation of esters with ketones and other esters (p. 239). It is interesting that the formation of cyclic ureides only occurs when a five- or six-membered ring can be formed.

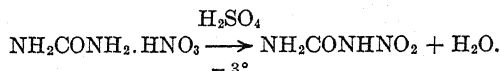
**Barbituric Acid.** Malonyl urea, the cyclic urea of malonic acid, is also known as barbituric acid. It is a weak acid in aqueous solution. We have previously seen in the case of the cyclic imides (p. 206) that a hydrogen on a nitrogen atom between the two carbonyl groups is acidic. This phenomenon is particularly marked in the case of the cyclic ureides. (A further discussion of these cyclic compounds will be reserved for Chap. XXVIII, p. 522).

The ureide of diethyl malonic acid is used in medicine as a soporific, and is known as **barbital** (**veronal**). It is made from the diethyl ester of diethyl malonic acid by a reaction exactly parallel to the one given above:

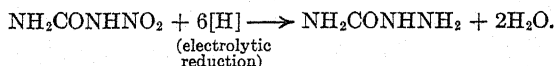


A variety of barbituric acid derivatives are marketed as soporifics; in these, other alkyl groups replace the ethyl group of barbital.

**Nitrourea and Semicarbazide.** One of the hydrogen atoms of urea may be replaced by a nitro group. This is accomplished by adding solid urea nitrate to concentrated sulfuric acid at  $-3^{\circ}$ :



Nitrourea is a crystalline solid which melts with decomposition at  $150^{\circ}$ . The chief importance of nitrourea lies in the fact that it is readily reduced to semicarbazide,  $\text{NH}_2\text{CONHNH}_2$ :

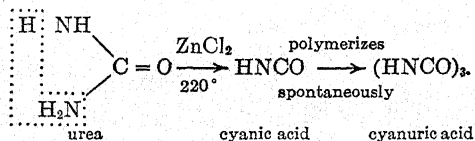


Semicarbazide is a crystalline solid melting at  $96^{\circ}$ ; it is easily soluble in water and alcohol, but insoluble in most organic solvents. Its basic strength is about that of the amines. It is usually prepared and marketed as the sulfate or hydrochloride,  $\text{NH}_2\text{CONHNH}_2 \cdot \text{HCl}$ , and in this form is widely used in the laboratory in the preparation of semicarbazones (p. 122).

**Alkyl Ureas.** Alkyl derivatives of urea in which one or more hydrogen atoms of the urea molecule are replaced by an alkyl group can be made by reactions very similar to those used in the preparation of urea except that an amine is substituted for ammonia. They are similar to urea in their properties and are crystalline solids.

### CYANIC ACID

If a molecule of ammonia is eliminated from urea, **cyanic acid**,  $\text{HNCO}$ , results. This substance polymerizes very easily to **cyanuric acid**, a compound in which three molecules of cyanic acid are joined in a ring. The polymer is the actual substance formed when urea is heated with zinc chloride:



**Preparation of Cyanic Acid from Cyanuric Acid.** Cyanuric acid is a white solid which is insoluble in almost all solvents. On heating it depolymerizes with the formation of cyanic acid. Cyanic acid is extremely unstable in aqueous solution, decomposing according to the following equation:

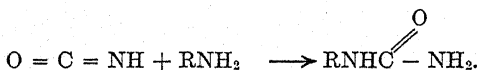
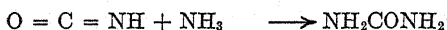
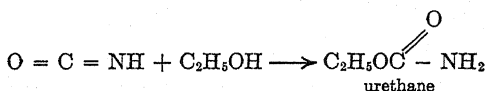
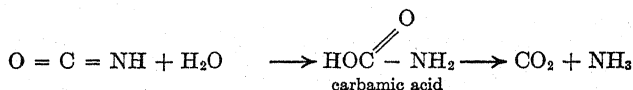


**Tautomerism of Cyanic Acid.** The formula for cyanic acid may be written in one of two forms,  $\text{HOC} \equiv \text{N}$  or  $\text{O} = \text{C} = \text{NH}$ ; the latter is called the isocyanic acid formula. Alkyl derivatives (esters) of the second form,  $\text{OCNR}$ , are known and are called alkyl isocyanates. Esters having the alkyl group attached to oxygen are unknown. Since the two possible formulas for cyanic acid differ by the position of a hydrogen atom and an unsaturated linkage, the problem presented by this substance is similar to the one considered in the previous chapter. However, unlike acetoacetic ester *no tautomeric isomers of cyanic acid* have been isolated. If the liquid cyanic acid or a solution of it contains both tautomeric forms as seems probable, the conversion of the one into the other must be very rapid. So rapid, indeed, as to make the isolation of isomers very difficult if not impossible. This type of tautomerism is more nearly like that of malonic ester (p. 239) than acetoacetic ester. The best information which is available as to the structure of cyanic acid comes from a comparison of the physical properties (particularly the absorption of light) of the acid and the esters (isocyanates  $\text{RNCO}$ ). Since the resemblance is close in many respects the formula  $\text{OCNH}$  is preferred to  $\text{HOCN}$ .

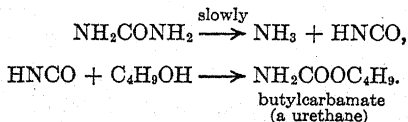
The tautomeric behavior of cyanic acid is not unique. On the contrary, there are numerous cases where we are unable to decide definitely on chemical grounds between two tautomeric formulas. Hydrocyanic acid is another example. Its structure might be  $\text{HC} \equiv \text{N}$  like that of a nitrile or  $\text{C} \equiv \text{NH}$  like that of an isonitrile. Since  $\text{HCN}$  resembles in physical properties the nitriles rather than the isonitriles, it is believed that the liquid contains chiefly the substance  $\text{HC} \equiv \text{N}$ . The amides might be written  $\text{RC} \begin{array}{l} \text{OH} \\ \diagup \\ \text{NH} \end{array}$  instead of  $\text{RCONH}_2$ . In this case, also, indirect evidence leads us to prefer one of the two tautomeric formulas, namely  $\text{RCONH}_2$ .

**Reactions of Cyanic Acid.** Cyanic acid reacts with water forming ammonia and carbon dioxide, with alcohols to form urethanes, with ammonia to form urea, and with a primary or secondary

amine to form a substituted urea. It is evident that in each reaction addition occurs at the  $C = NH$  group and a hydrogen atom becomes attached to the  $NH$  group.

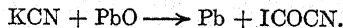


Urea itself may sometimes be used as a source of nascent cyanic acid, since urea on losing a molecule of ammonia passes into cyanic acid. Thus, if urea is heated with normal butyl alcohol for some hours, the small amount of cyanic acid which is slowly formed reacts with the butyl alcohol and forms a urethane.

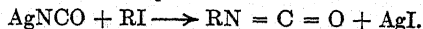


This is a convenient method of preparing certain urethanes.

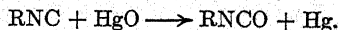
**The Cyanates.** The salts of cyanic acid are known as the cyanates. They can be prepared by bringing together the gaseous acid and a base, or more conveniently by the oxidation of cyanides. For example, potassium cyanate can be prepared by the oxidation of potassium cyanide with lead oxide:



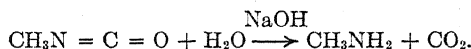
The isocyanates are prepared by the action of an alkyl iodide on potassium or better silver cyanate:



Another method of preparing alkyl isocyanates is by the oxidation of an isonitrile:



The alkyl isocyanates are volatile liquids with a very disagreeable odor. They are somewhat unstable, tending to polymerize to trimers (esters of isocyanuric acid). (It will be recalled that alkyl esters of cyanic acid,  $\text{ROCN}$ , are unknown (p. 253).) The isocyanates are hydrolyzed by warming with alkali with the formation of a primary amine and carbon dioxide. This fact proves that the alkyl group is attached to nitrogen:

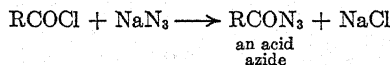


The isocyanates combine with alcohol to form alkyl urethanes and with amines to form disubstituted ureas:

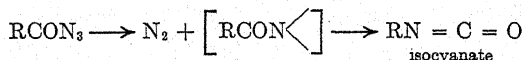


A few of the isocyanates (in which R is a large group) are used to identify alcohols and amines, since the urethanes and the disubstituted ureas obtained are crystalline solids which have definite melting points.

**Isocyanates from Acid Azides.** An important reaction for the preparation of isocyanates (or their addition products) from acids involves a peculiar compound known as an **acid azide**, an acyl derivative of hydrazoic acid,  $\text{HN}_3$ . These compounds may be prepared by the interaction of acid chlorides and sodium azide.



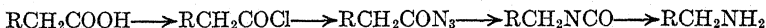
The acid azides are unstable and reactive compounds. On heating they lose nitrogen gas and undergo a remarkable shift of atoms or **molecular rearrangement**, known as the **Curtius rearrangement**.



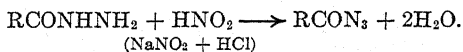
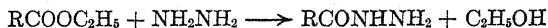
The compound  $\text{RCON} \begin{array}{c} \diagup \\ \diagdown \end{array}$  which is probably the first product contains a monovalent nitrogen atom and has therefore only a momentary existence. By the shift of the alkyl group, all the atoms can assume their normal valency.

The importance of the Curtius reaction lies in the fact that the

resulting isocyanate can be transformed by the reactions given above into a primary amine, a urethane, or a urea derivative. Thus, by the use of the azides, the same type of degradation may be accomplished as by the Hofmann reaction. For example:



The acid azides may also be formed by the action of nitrous acid on the acyl derivatives of hydrazine,  $\text{NH}_2\text{NH}_2$ . These compounds in turn may be prepared by the action of hydrazine on esters or amides.



**Fulminic Acid.** A very unstable compound isomeric with cyanic acid is fulminic acid, for which the following formula must be written:  $\text{CNOH}$ . The

electronic formula is perhaps the following:  $\text{H} : \ddot{\text{O}} : \text{N} :: \text{C} :$  It should be

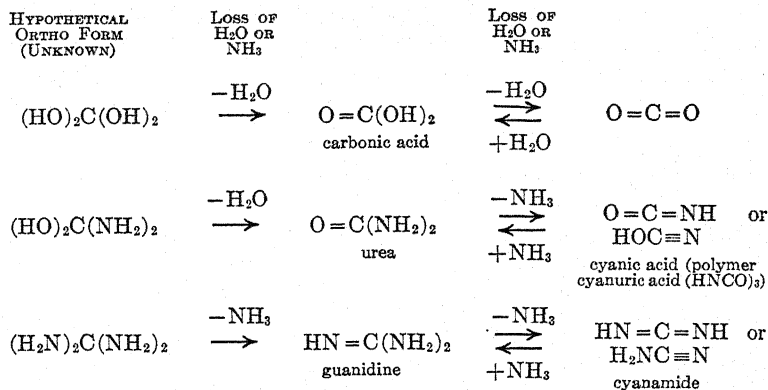
noted that although this substance is an isomer of cyanic acid, it is not a tautomeric form, since it can not pass into cyanic acid by a mere transfer of hydrogen. It differs from cyanic acid in the order in which the carbon, nitrogen, and oxygen atoms are arranged. The mercury salt of this acid has been known for a long time because it is formed when mercuric nitrate, alcohol, and nitric acid are brought together. It is a powder, insoluble in alcohol and water. When dry it is a powerful explosive, detonating with a very slight blow. It is known as **mercury fulminate** and is used extensively in the manufacture of priming caps which explode when struck a sharp blow. A similar compound is **silver fulminate**, prepared in the same way from silver nitrate, nitric acid, and alcohol. The free fulminic acid can be prepared from these salts. It is a very unstable, volatile compound which is extremely poisonous.

#### OTHER AMMONIA DERIVATIVES OF CARBONIC ACID

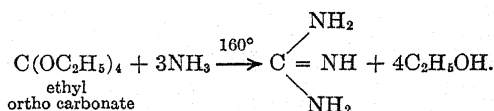
If we imagine that all the hydroxyl groups of the hypothetical ortho carbonic acid,  $\text{C}(\text{OH})_4$ , are replaced by  $\text{NH}_2$  groups, the compound  $\text{C}(\text{NH}_2)_4$  would result. This substance is unknown, but the compound which would result from it by loss of a molecule of ammonia is a well known and an important substance. It is **guanidine**,  $\text{C}(=\text{NH})(\text{NH}_2)_2$ . By further loss of ammonia, guanidine passes into another interesting substance, **cyanamide**,  $\text{NH}_2\text{CN}$ . We thus have a series of compounds each formed from the other by loss of ammonia. This series is analogous to

that formed from the dehydration products of ortho carbonic acid:

## RELATIONSHIP OF DERIVATIVES OF CARBONIC ACID

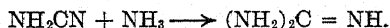


**Guanidine.** We have just seen that guanidine is related to the ortho form of carbonic acid. Therefore, it is not surprising that it may be prepared by the action of ammonia on the ethyl ester of ortho carbonic acid:



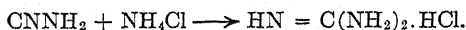
This tetraethyl ester of the unknown ortho form of carbonic acid may be prepared by the action of potassium ethylate on carbon tetrabromide. (This reaction is exactly analogous to the method of preparation of the esters of orthoformic acid [p. 133].)

Other more convenient methods of preparing guanidine are available. It can be prepared by the addition of ammonia to cyanamide:

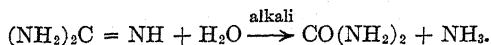


Guanidine is a colorless, very hygroscopic, crystalline solid which is exceedingly soluble in water. Surprisingly enough it is as strong a base as sodium hydroxide (see Fig. 20). It is usually prepared and used in the form of one of its salts. For example, in the preparation of guanidine from cyanamide the source of the

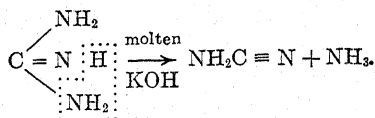
ammonia is ammonium chloride, and the hydrochloride of guanidine is the actual product:



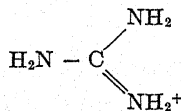
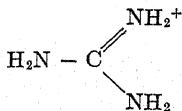
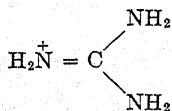
**Reactions of Guanidine.** Guanidine is readily hydrolyzed with the formation of urea and ammonia. The reaction is catalyzed by the presence of bases:



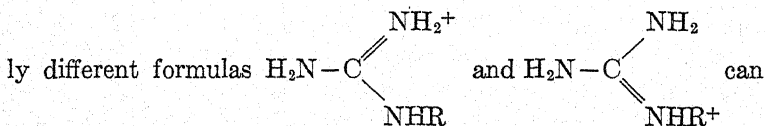
When guanidine carbonate is fused with potassium hydroxide a molecule of ammonia is lost and cyanamide is formed:



**Structure of Guanidinium Ion.** The salts of guanidine such as guanidinium chloride,  $(\text{NH}_2)_2\text{CNH}_2\text{Cl}$ , contain the ion  $[(\text{NH}_2)_2\text{CNH}_2]^+$ . For such an ion, three formulas might be written:



In the ion derived from guanidine itself, these appear identical but if one hydrogen atom is replaced by an alkyl group, two clearly



be written. All these formulas differ in the position of a double linkage but unlike the isomeric formulas we have hitherto encountered, *they may be transformed into each other without any shift of an atom or group. No isomers corresponding to these formulas have ever been isolated.* This is not surprising when we realize that if such isomers existed they would differ *only* in the position of a linkage, that is, of valency electrons. No isomers have ever been found in all of organic chemistry whose structural formulas differ *only* by the position of electrons. Instead, it has been found that when

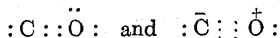
such isomeric formulas may be written the compound in question is usually remarkably stable. Thus the guanidinium ion has much less tendency to lose a proton ( $H^+$ ) than has the ammonium ion. In other words, guanidine is a remarkably strong base (approximately 10,000 times stronger than the amines).

**Resonance.** An explanation of the marked stability of the guanidinium ion and other compounds of this general type has been advanced within the last decade. To understand this explanation fully one must be familiar with the application of wave-mechanics to the electron theory of valence. The essential conclusions can be stated rather simply, however. If a molecule can have two or more structures which differ only by the shift of valency electrons representing unsaturation, then in most instances, the actual structure does not correspond to any of the formulas which are written but partakes to some extent of the properties of all; the compound has a greater stability than corresponds to any of the formulas. The molecule is then said to exhibit **resonance**. It can not be represented accurately by any one formula for it is a resonance-hybrid of two or more structures.

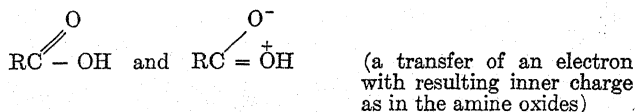
**Resonance Energy Shortens Links.** One manifestation of resonance energy is the shortening of the links between atoms. The energy which binds the atoms is increased by resonance and the atoms come nearer together. By means of the X-ray analysis of crystals and the diffraction of electrons by gases it is possible to determine the inter-nuclear distances in many compounds. In carbon compounds in which there is no resonance, the distance between the atoms is remarkably constant for a given type of linkage. Thus the distance between atomic centers in the normal C—N bond is 1.48 Ångström units ( $A = 10^{-8}$  cm.) and for C=N, 1.28Å. The structure of the guanidinium ion has been found by X-ray analysis of the solid salts to be a perfectly symmetrical arrangement of three  $NH_2$  groups around a central carbon atom with a distance between the carbon and nitrogen atoms of only 1.18Å. This corresponds to a large resonance energy. It should be noted further that the symmetry revealed by the X-ray analysis of the crystalline salt excludes any formula for the ion in which one nitrogen atom is bound differently from the other two.

**Other Examples of Resonance.** We shall meet with the phenomenon of resonance several times again. Of the compounds already considered, a few

which exhibit marked resonance may be considered at this point. Carbon monoxide has a very large resonance energy, the two resonating structures being

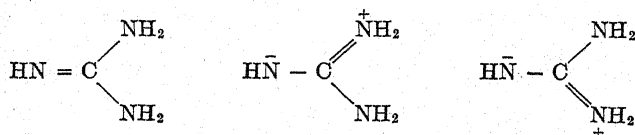


The ion of the carboxyl group  $RCOO^-$ , is a resonance-hybrid of the two structures  $RC(=O)O^-$  and  $RC(O^-)=O$ . The carboxylic group itself also exhibits resonance, the two forms being:

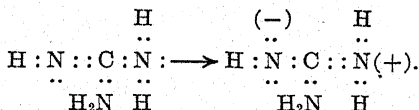


The first (represented by the usual formula) is more stable and contributes much more than the other to the resonance. The two structures of the ion  $RCOO^-$  on the other hand are equivalent. In general, the more nearly equivalent the resonating structures the greater the resonance energy. Therefore, the ion of the carboxylic group has greater resonance energy than the free acid. Hence, the process of ionization is favored by resonance.

Guanidine itself (the free base) also exhibits resonance but, as in the case just mentioned, the resonance energy is much less than with the ion. Therefore, salt formation is favored by resonance. The *relatively* weak resonance of the free base involves the following structures:

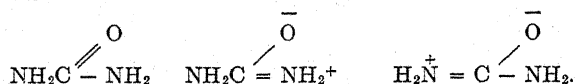


The shift from the first formula on the left to the second involves the following electronic change:



The distribution of plus and minus signs on the formula to the right follows from the fact that the octet of the left hand nitrogen atom contains six electrons contributed by nitrogen. This is one more than the normal, hence the negative sign. Similarly the nitrogen atom on the right contributes only four electrons to the octet, the others coming two from two hydrogen atoms and two from carbon. Hence this nitrogen atom may be considered to have *lost* an electron and to carry a positive charge. Unlike the resonating structures of the *guanidinium ion* these structures are not equivalent, the first being more

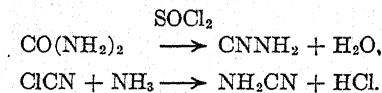
stable than the others. Urea also exhibits resonance, the formulas again not being equivalent:



The C—N distance in urea is only shortened from the normal 1.42A to 1.37A.

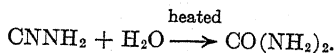
**Resonance in Chelate Rings.** In the last chapter, it was pointed out that in certain metallic derivatives of enols, chelate rings were present. A similar ring appears to be present also in the enol form itself (*i.e.*, the hydrogen compound). This appears to be the case although the formation of this ring involves the hydrogen atom having a co-valence of two. The stability of this ring (which, however, is not great in the case of the hydrogen compound) is probably largely due to resonance. If the formula on p. 237 is examined it will be seen that the double bonds may be shifted without moving any atom or group. The two formulas which can be written represent the two resonating structures. The possibility of resonance between these forms is responsible for the increased stability of such rings. This explains why *in this instance* hydrogen becomes part of a ring system although in general there is no ring formation involving divalent hydrogen. For example, when an hydroxyl group and a ketone group are separated by two saturated carbon atoms no chelation occurs.

**Cyanamide.** Cyanamide,  $\text{NH}_2\text{C} \equiv \text{N}$ , may be regarded as the nitrile of carbamic acid,  $\text{NH}_2\text{COOH}$ . As in the case of cyanic acid and many other compounds, the position of the hydrogen atom in this compound can not be considered as definitely established. Many of the reactions of the substance correspond to the formula  $\text{NH} = \text{C} = \text{NH}$ , rather than  $\text{NH}_2\text{C} \equiv \text{N}$ , and the liquid may be a mixture of both forms. Cyanamide may be prepared from guanidine by the method given in a preceding paragraph. It is also formed from urea by the action of dehydrating agents, and by the interaction of ammonia and cyanogen chloride:

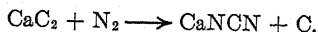


Cyanamide is a deliquescent, colorless solid melting at 41°–42°. It is soluble in water, alcohol, and ether. It has very weakly basic properties; even its salts with strong acids are completely hydrolyzed by water. It is also a weak acid, and forms sodium and potassium salts which are stable in aqueous solution. Free cyanamide is difficult to keep in a pure state as it passes over into

dicyandiamide in the presence of moisture. On hydrolysis cyanamide yields urea:

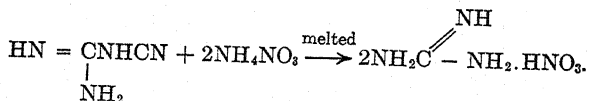
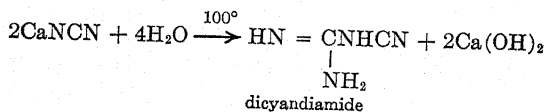


**Salts of Cyanamide.** Calcium cyanamide is a substance of great commercial importance. It is prepared by heating calcium carbide and nitrogen in an electric furnace:



The crude calcium cyanamide thus formed is often called "lime nitrogen," and is used as a fertilizer. In the soil it first undergoes a hydrolysis to cyanamide, which in turn is hydrolyzed to urea and finally to ammonia.

In addition to the use of calcium cyanamide as a fertilizer, it can also be used as the starting point for the preparation of a number of compounds which we have been considering in this chapter. For example, guanidine can be prepared from it through the intermediate formation of a compound known as dicyandiamide. This is illustrated by the following reactions:



Dicyandiamide is a colorless, crystalline compound melting at 205°, rather soluble in alcohol and water. It has no pronounced acid or basic properties. On reduction it yields guanidine and methylamine.

### QUESTIONS AND PROBLEMS

- Construct a chart showing reactions involved in transforming calcium carbide into: cyanamide, urea, guanidine hydrochloride, ethyl carbonate, urethane.
- Complete the following equations: (a)  $\text{CO}(\text{NH}_2)_2 + \text{HONO}$ ; (b)  $(\text{C}_2\text{H}_5\text{O})_2\text{C} = \text{O} + \text{NH}_3$ ; (c)  $\text{C}_2\text{H}_5\text{N} = \text{C} = \text{O} + \text{C}_2\text{H}_5\text{OH}$ ; (d)  $\text{COCl}_2 + \text{CH}_3\text{NH}_2$  (in excess); (e)  $\text{CH}_3\text{CH}_2\text{COOH} + \text{CH}_3\text{N}_2$ ; (f)  $\text{CO}(\text{NH}_2)_2 + \text{CH}_3\text{COCl}$ ; (g)  $\text{CH}_3\text{CH}_2\text{N} = \text{C} = \text{O} + \text{CH}_3\text{NH}_2$ .
- Show by equations how you would prepare the following compounds: (a)  $(\text{CH}_3)_2\text{NCOOC}_2\text{H}_5$ ; (b)  $\text{CH}_3\text{NHCONHCH}_3$ ; (c)  $\text{C}_2\text{H}_5\text{NHCOOC}_2\text{H}_5$ ; (d)  $\text{CNNH}_2$ ; (e)  $\text{NH}_2\text{CONHNH}_2$ .
- A water solution is known to contain a considerable amount of sodium chloride and any one of the following: acetamide, ammonium acetate or urea. By means of what experiments could you decide between the three possibilities?

5. What reactions of urea are of importance in its clinical determination?
6. Write equations showing several methods of preparing amides. What is the commercial method of manufacturing urea? Could a similar procedure be used for preparing acetamide?
7. Outline procedures for preparing the following compounds from urea: (a) cyanic acid; (b) *n*-butylbarbituric acid; (c) isopropyl carbonate; (d) guanidine.
8. Write the formula for methyl guanidine and devise a method for its preparation.

9. If  $(\text{CH}_3)_2\text{N}-\overset{\text{NC}_2\text{H}_5}{\text{C}}=\text{N}(\text{CH}_3)_2$  is treated with ethyl iodide, tetramethyl-diethyl-guanidinium iodide is formed. How would you prepare the free base and what would you predict as to its properties? Would you expect to be able to prepare an isomeric iodide by the action of methyl iodide on

$(\text{C}_2\text{H}_5)_2\text{N}-\overset{\text{NCH}_3}{\text{C}}=\text{N}(\text{CH}_3)_2$ ? Give the reasons for your answer.

10. The imino derivatives of aldehydes and ketones  $\text{R}_2\text{C}=\text{NH}$  are very readily hydrolyzed to ammonia and the carbonyl compound. Why is guanidine so much more resistant to hydrolysis than these compounds? Would you expect the amidines to be like the imino derivatives of ketones or like guanidine? Why? What would you predict as to the basic strength of

$(\text{CH}_3\text{NH})_2\text{C}=\text{NH}$ ,  $\text{CH}_3\overset{\text{NH}}{\text{C}}=\text{NH}_2$ ,  $\text{CH}_3\overset{\text{NH}}{\text{C}}=\text{CH}_3$ ,  $\text{CH}_3\text{CONHCH}_3$ ,  $\text{CH}_3\text{NH}-\text{COOC}_2\text{H}_5$ ,  $\text{CH}_3\text{NHCONHNH}_2$ . Give your reasons.

11. Write the steps involved in the following transformations: (a)  $\text{RCH}_2\text{COOH}$  to  $\text{RCH}_2\text{NH}_2$ ; (b)  $\text{RCH}_2\text{COOH}$  to  $\text{RCH}_2\text{NHCOOCH}_3$ ; (c)  $\text{NH}_2\text{CONH}_2 + \text{ROH}$  to  $\text{NH}_2\text{COOR}$ .

## CHAPTER XV

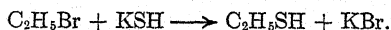
### COMPOUNDS CONTAINING SULFUR

In many of the preceding chapters, we have been concerned with substances which may be regarded as derivatives of water, ammonia, or carbonic acid. We shall now consider some organic compounds which are derivatives of hydrogen sulfide or related to carbon disulfide ( $\text{CS}_2$ ). Since sulfur occurs immediately under oxygen in the same group of the periodic table, there is a marked similarity between sulfur and oxygen compounds. Perhaps the greatest difference between the two elements lies in the fact that in many substances sulfur has a valence greater than two. Thus, we shall find large classes of organic sulfur compounds in which the element has a higher valence and for which no analogy exists in the compounds containing oxygen. However, the organic sulfur compounds in which the valence of sulfur is two, closely parallel the corresponding oxygen compounds. Because of this close analogy much of the chemistry of simple sulfur compounds may be easily related to information already acquired.

#### DERIVATIVES OF HYDROGEN SULFIDE

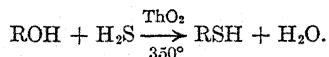
The monoalkyl derivatives of hydrogen sulfide,  $\text{RSH}$ , are known as mercaptans; they are the sulfur analogs of the alcohols. The sulfur analogs of the ethers are the dialkyl derivatives of hydrogen sulfide,  $\text{RSR}$ ; they are known as the alkyl sulfides or thioethers.

**Mercaptans.** The commonest method of preparing the mercaptans is by the interaction of an alkyl halide and the monopotassium salt of hydrogen sulfide in alcoholic solutions. This reaction is analogous to the preparation of an alcohol by the hydrolysis of an alkyl halide:



Since an alkyl halide is prepared from an alcohol, we have here an indirect method of replacing an hydroxyl group by a **sulfhydryl group** ( $\text{SH}$ ). A direct method of accomplishing the interchange of these groups consists in passing the vapors of an alcohol

mixed with hydrogen sulfide over certain catalysts at an elevated temperature:

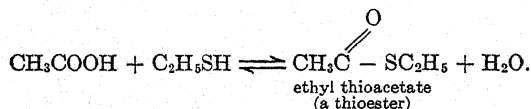


**Properties of the Mercaptans.** The boiling points of the simpler mercaptans are given in the table. Ethyl mercaptan is a colorless liquid with an intensely disagreeable odor. It can be detected by its odor in extraordinarily small amounts. Even the lower members of the series are but slightly soluble in water. They dissolve in sodium hydroxide solution, however, with the formation of a sodium salt which is appreciably hydrolyzed. The mercaptans are thus somewhat more acidic than the corresponding alcohols.

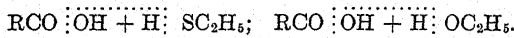
PHYSICAL PROPERTIES OF THE SIMPLER MERCAPTANS

NAME	FORMULA	BOILING POINT
Methyl mercaptan	$\text{CH}_3\text{SH}$	6°
Ethyl mercaptan	$\text{C}_2\text{H}_5\text{SH}$	37°
<i>n</i> -Propyl mercaptan	$\text{C}_3\text{H}_7\text{SH}$	68°
Isopropyl mercaptan	$(\text{CH}_3)_2\text{CHSH}$	59°

**Formation of Thioesters.** The mercaptans react with organic acids with the elimination of a molecule of water. The resulting compound is a sulfur analog of an ester, and is known as a thioester. As in the case of the formation of esters from alcohols, the reaction is a balanced one and does not go to completion.



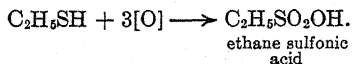
The fact that water is eliminated in this reaction and not hydrogen sulfide is of considerable interest. Formerly, this reaction was considered as convincing evidence that in the analogous reaction between an alcohol and an acid, water is formed by the union of the hydroxyl group of the acid and the hydrogen atom of the alcohol. The analogy may be summarized thus:



The direct proof of the origin of water during esterification has been considered on page 98.

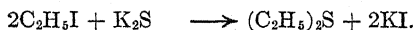
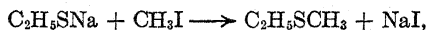
**Sulfonic Acids.** In their behavior towards oxidizing agents, mercaptans are entirely different from alcohols. The action of a powerful oxidizing agent increases the valence of the sulfur instead

of removing hydrogen. The final product of such an oxidation is a substance known as a sulfonic acid:



The sulfonic acids may be regarded as derivatives of sulfuric acid in which one hydroxyl has been replaced by an alkyl group. They differ greatly from the esters of sulfuric acid (*e.g.*,  $\text{C}_2\text{H}_5\text{OSO}_3\text{H}$ ), which are the results of the replacement of a hydrogen atom in sulfuric acid by an alkyl group. Unlike the esters of sulfuric acid, the sulfonic acids are not hydrolyzed by boiling with alkali. The sulfonic acids are strong acids comparable with the mineral acids. They are crystalline solids, easily soluble in water.

**The Alkyl Sulfides.** The sulfur analogs of the ethers are the alkyl sulfides or *thio-ethers*. The methods of preparation are illustrated by the following equations. The first can be used for the preparation of mixed sulfides, the second only for the synthesis of symmetrical compounds:



The physical properties of some of the simpler alkyl sulfides are given in the table. The alkyl sulfides have a disagreeable odor, though not so penetrating as that of the mercaptans. **Allyl sulfide**,  $(\text{CH}_2 = \text{CHCH}_2)_2\text{S}$ , is the chief constituent of oil of garlic. They are all insoluble in water and soluble in organic solvents. They show no acidic properties, but form addition compounds with a number of metallic salts. These addition compounds are usually insoluble in water. An example of such a compound is the addition product of ethyl sulfide with mercuric chloride,  $(\text{C}_2\text{H}_5)_2\text{S} \cdot \text{HgCl}_2$ .

**Mustard Gas.** During the World War a dihalogen derivative of an alkyl sulfide was used extensively as a poisonous gas. This is the compound known as  $\beta$ ,  $\beta'$ -dichloroethyl sulfide:

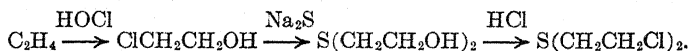


It is a liquid which boils at  $215^\circ$ . It is insoluble in water but penetrates the skin when in contact with it, and in a few hours produces a very painful burn and blister. Because of this action it was an extremely potent war gas. The exposure of a considerable portion of the body to the fumes of this liquid for a short time will produce a burn sufficient to cause serious injury and often

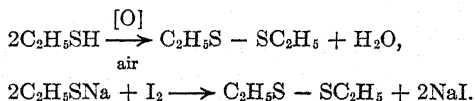
death. The compound can be prepared by the direct interaction of ethylene and sulfur chloride according to the following equation:



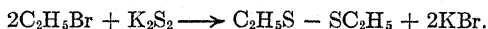
This is a peculiar reaction, and the mechanism of it is not clearly understood. A more orthodox method of preparing this sulfide is indicated by the following series of reactions which starts with ethylene:



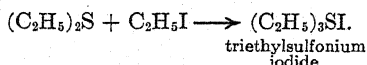
**Disulfides.** Cautious oxidation of the mercaptans may result in the formation of a disulfide, RSSR, instead of a sulfonic acid. For example, slow oxidation by the air of ethyl mercaptan, or the action of iodine on an alkaline solution produces diethyl disulfide:



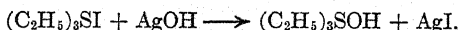
Another method of preparing disulfides is to heat an alkyl halide with potassium disulfide:



**Sulfonium Salts.** Alkyl sulfides combine with one molecule of an alkyl halide to form a tri-alkyl sulfonium salt. These compounds are crystalline solids which are soluble in water:



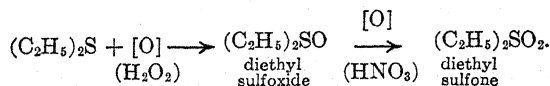
The corresponding base may be prepared by the action of silver hydroxide:



The sulfonium bases are strong bases comparable to the quaternary ammonium hydroxides. They may be obtained as deliquescent crystalline solids. A brief discussion of these compounds in an earlier chapter (p. 169) emphasized that the essential reaction is the formation of the ion  $\text{R}_3\text{S}^+$ . The salts are thus aggregates of the ions  $\text{R}_3\text{S}^+$  and  $\text{X}^-$ , and the corresponding hydroxides are composed of the ions  $\text{R}_3\text{S}^+$  and  $\text{OH}^-$ .

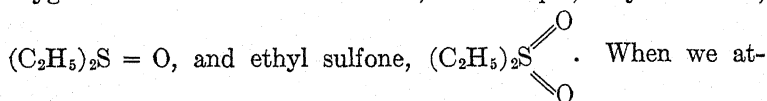
**Sulfoxides and Sulfones.** Oxidation of the alkyl sulfides with such reagents as hydrogen peroxide or nitric acid causes the addition of one or two atoms of oxygen without disruption of the molecule. The first product is called a **sulfoxide** and has

the general formula  $R_2SO$ ; the final product is a sulfone,  $R_2SO_2$ :

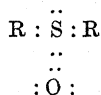


The sulfoxides and sulfones are usually crystalline solids. Dimethyl sulfone melts at  $109^\circ$ ; the liquid boils at  $238^\circ$ .

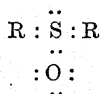
**Structure of Sulfones.** The structural formulas of the sulfoxides and sulfones are often written with a double linkage between the oxygen atoms and the sulfur atoms, for example, ethyl sulfoxide,



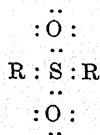
tempt to write electronic formulas corresponding to these formulas, we immediately encounter difficulties. In the case of the sulfoxide, the electronic equivalent of the formula with a double linkage would contain a sulfur atom with ten electrons in the outer shell (four are common with the oxygen):



But there are many reasons to believe that sulfur, like other elements of low atomic number, can have only a maximum of eight electrons in the outer shell. The electronic formula in which both sulfur and oxygen have a complete octet of electrons (but no more), is as follows:

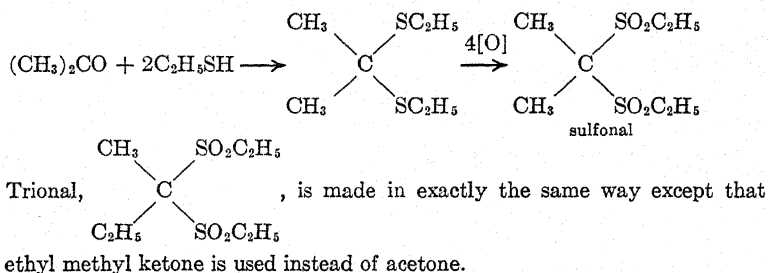


It is impossible to write the electronic equivalent of the sulfone formula which has two double bonds except by putting twelve electrons in the outer shell of sulfur. The correct electronic formula for a sulfone is, therefore, as follows:



It is evident that the linkage between sulfur and oxygen in the sulfones and sulfoxides is very similar to that between nitrogen and oxygen in the amine oxides. The same is true of two of the three oxygen atoms of the sulfonic acids. It is misleading to write the conventional double bond in the formulas of these compounds; and it has been suggested that such formulas as the following be employed:  $R_2\overset{+}{S}-\overset{-}{O}$  or  $R_2S\rightleftharpoons O$ ; compare the amine oxides (p. 167). It seems quite unnecessary to express the electronic arrangement in the usual structural formula, and such noncommittal formulas as the following will be found ample for most purposes:  $R_2SO$ ,  $R_2SO_2$ ,  $RSO_2OH$ .

**Disulfones as Drugs.** Two sulfur compounds which are prepared because of their use as soporifics are sulfonal and trional. Both of these are colorless solids, slightly soluble in water. They are prepared by first forming the sulfur analog of an acetal from a ketone and a mercaptan, and then oxidizing the product to the corresponding sulfone. The method is illustrated by the steps in the synthesis of sulfonal which are as follows:

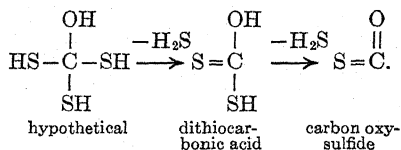


#### DERIVATIVES OF THE SULFUR ANALOGS OF CARBONIC ACID

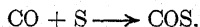
In the last chapter a variety of compounds were discussed which were derived from the ortho form of carbonic acid by the replacement of one or more hydroxyl groups by  $\text{NH}_2$  groups (p. 257). If we similarly imagine that the hydroxyl group of orthocarbonic acid is replaced by the  $\text{SH}$  group, various types of interesting compounds result.

Some of these may be regarded as derived from the ortho form of carbon disulfide, the sulfur analog of carbon dioxide, while others are related to carbon oxysulfide,  $\text{COS}$ .

**Carbon Oxsulfide.** The following series of compounds may be regarded as derived from a hypothetical ortho compound,  $\text{HOC}(\text{SH})_3$ , by progressive loss of hydrogen sulfide:

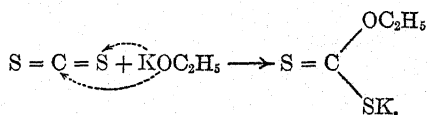


Carbon oxsulfide,  $\text{COS}$ , is a colorless gas which liquefies at  $-47.5^\circ$ . It can be formed by the union of sulfur and carbon monoxide at a low red heat:



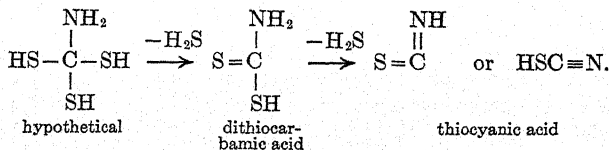
**The Xanthates.** Dithiocarbonic acid, of which carbon oxsulfide is the anhydride, is known only in the form of its salts or esters. The half esters which have an alkyl group attached to oxygen are known as the **xanthic acids** or **xanthogenic acids**. They have the

general formula  $\text{ROC}=\text{SH}$ ; the corresponding salts,  $\text{ROC}=\text{SNa}$ , are known as the **xanthates**. They are formed by the addition of an alcoholate to carbon disulfide:



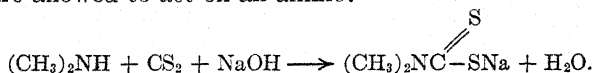
The same reaction proceeds if an alcohol, potassium hydroxide, and carbon disulfide are mixed. A very important xanthate is that formed from cellulose; this will be referred to in connection with the manufacture of artificial silks.

**Dithiocarbamic Acids.** The following series of substances containing sulfur and nitrogen may be regarded as derived from the ortho compound  $\text{NH}_2\text{C}(\text{SH})_3$ :



This series is analogous to the one which includes carbamic acid and cyanamide (Chap. XIV).

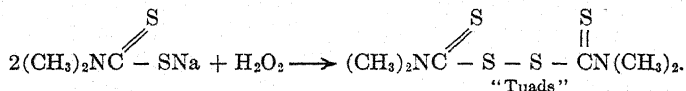
Dithiocarbamic acid is unknown in the free state, but the salts of its alkyl derivatives are readily formed if carbon disulfide and alkali are allowed to act on an amine:



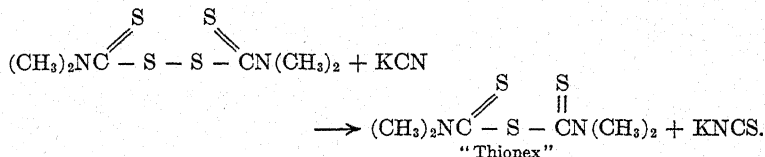
The salts of the dialkyl-dithiocarbamic acids are of importance in the preparation of two substances which are used in large quantities in the rubber industry.

**Accelerators of Vulcanization of Rubber.** A number of organic sulfur compounds are used in large quantities in the rubber industry to accelerate the process of vulcanization (p. 75). About twenty-five years ago, it was discovered that certain organic nitrogen compounds greatly decreased the time required for vulcanizing rubber. One of the compounds first used was thio-carbanilide (p. 273). It is now known that at least ten different classes of organic compounds will accelerate the vulcanization process. All the accelerators contain either sulfur or nitrogen or both elements. Among the sulfur-free accelerators may be mentioned hexamethylenetetramine (p. 129), aliphatic amines, derivatives of guanidine containing the phenyl group,  $\text{C}_6\text{H}_5-$  (p. 339), and condensation products of aldehydes and amines.

Two sulfur compounds which are capable of bringing about rapid vulcanization at a particularly low temperature are closely related to dithiocarbamic acid. "Tuads" is the trade name of the disulfide formed by oxidizing the dithiocarbamic acid prepared from dimethylamine. (The interaction of carbon disulfide and dimethylamine was considered above.)



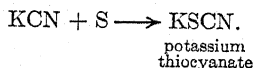
When the product known as "Tuads" is treated with potassium cyanide, an atom of sulfur is removed. The monosulfide which is formed is sold under the name of "Thionex":



The introduction of accelerators into the rubber industry has decreased the cost of manufacture of rubber articles by decreasing the time of vulcanization, which in turn has decreased the investment in machinery and plant. A finished product of far superior and more uniform quality has also been produced. Very little is known about the action of accelerators. Indeed,

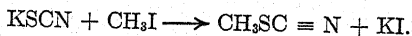
the very nature of vulcanization itself is under dispute. The process probably consists in a further polymerization, and at the same time a union of the sulfur atom with some of the unsaturated linkages of the rubber molecule. It is not at all clear why certain types of organic compounds should be such powerful catalysts for these changes.

**Thiocyanic Acid and the Thiocyanates.** Thiocyanic acid, HSCN, is the sulfur analog of cyanic acid. It is prepared from its salts, which are readily formed by heating cyanides with sulfur (compare the preparation of cyanates, p. 254):



Thiocyanic acid is a white crystalline solid melting at 5° to a yellow liquid which soon polymerizes. The acid is readily soluble in water. The potassium, sodium, and ammonium salts are soluble; a number of those with the heavy metals are insoluble. The ferric salt,  $\text{Fe}(\text{CNS})_3$ , is formed on bringing together a soluble ferric salt and a soluble thiocyanate. Its characteristic red color serves as a very sensitive test for ferric ions. The insoluble mercuric salt,  $\text{Hg}(\text{SCN})_2$ , burns when ignited forming a very long voluminous ash. This striking phenomenon has been called the formation of "Pharaoh's serpents."

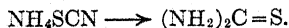
Unlike cyanic acid, the alkyl derivatives of both the tautomeric forms of thiocyanic acid have been prepared. They are the so-called **normal esters**,  $\text{R} - \text{S} - \text{C} \equiv \text{N}$ , and the **isoesters**,  $\text{S} = \text{C} = \text{NR}$ . Thiocyanic acid itself is a strong acid in dilute aqueous solution and probably has the structure  $\text{HSC} \equiv \text{N}$ , although it may be a mixture of the two tautomeric forms. The normal esters are prepared by the action of an alkyl halide on potassium thiocyanate:



On heating to a high temperature the normal esters rearrange with the formation of the isoesters.

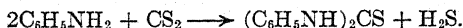
**Alkyl Isothiocyanates or Mustard Oils.** The isothiocyanates, RNCS, can be readily prepared by the rearrangement of the normal thiocyanates or by the action of sulfur on the isonitriles. They derive the name of mustard oils because of the fact that the allyl compound,  $\text{CH}_2 = \text{CHCH}_2\text{NCS}$ , is the active principle in mustard. All the alkyl isothiocyanates have a sharp odor and biting taste.

**Thiourea or Thiocarbamide.** The sulfur analog of urea can be formed by melting the ammonium salt of thiocyanic acid; the reaction is parallel to Wöhler's classical synthesis of urea:



Thiourea is a crystalline compound melting at  $180^\circ$  and soluble in water.

**Thiocarbanilide.** Diphenylthiourea or thiocarbanilide,  $\text{S} = \text{C}(\text{NHC}_6\text{H}_5)_2$ , is one of the commonest organic sulfur compounds. It is prepared from aniline,  $\text{C}_6\text{H}_5\text{NH}_2$ ; this is a primary amine which contains the phenyl group ( $\text{C}_6\text{H}_5$ ) instead of an alkyl group. By heating carbon disulfide and aniline above  $100^\circ$ , the following reaction takes place:



Thiocarbanilide is a crystalline solid melting at  $154^\circ$ . Its use as an accelerator of rubber vulcanization has been noted previously. The sulfur atom in diphenylthiourea may be replaced by the  $=\text{NH}$  group by heating the compound with lead oxide and ammonia. The product is a guanidine derivative containing two  $\text{C}_6\text{H}_5$ -groups, and hence is known as **diphenylguanidine**,  $\text{HN} = \text{C}(\text{NHC}_6\text{H}_5)_2$ . It has also been used in very large quantities as an accelerator in rubber vulcanization.

#### ORGANIC DERIVATIVES OF THE HYDRIDES OF OTHER ELEMENTS

We have noted that there are classes of organic compounds corresponding to the hydrides of nitrogen ( $\text{NH}_3$ ), sulfur ( $\text{H}_2\text{S}$ ), and oxygen ( $\text{H}_2\text{O}$ ). Similarly, alkyl derivatives of the hydrides of many other elements are known. If we follow down the sixth group of the periodic table, we find organic compounds of selenium and tellurium quite comparable to the sulfur and oxygen compounds. In the fifth group of the table under nitrogen are phosphorus, arsenic, and antimony, and we might readily predict the existence of a variety of compounds analogous to the nitrogen compounds, but containing one of these elements in place of the nitrogen atom. Many such substances are indeed known. In general the differences among the organic compounds of these other elements and their more common prototypes (containing nitrogen or oxygen) reflect the differences among the elements themselves. With the exception of the zinc alkyls (p. 28) and the organo-magnesium compounds (Grignard reagents), the organic chemistry of the elements other than oxygen, nitrogen, sulfur, and the halogens, is not of sufficient importance to warrant consideration in an elementary book.

## QUESTIONS AND PROBLEMS

1. Write balanced equations showing the preparation of the following compounds: isopropyl mercaptan, di-*n*-propyl sulfone, thiourea, trimethylsulfonium hydroxide, trional, "mustard gas," isopropyl ethyl sulfide.

2. List the common classes of organic sulfur compounds and oxygen compounds which are analogous to each other. Using general equations, illustrate a typical method of preparation of each class.

3. Complete the following equations: (a)  $\text{CS}_2 + \text{KOC}_2\text{H}_5$ ; (b)  $\text{CH}_3\text{NC} + \text{S}$ ; (c)  $\text{CH}_3\text{COCH}_3 + \text{C}_2\text{H}_5\text{SH}$ ; (d)  $\text{CH}_3\text{SC}_2\text{H}_5 + [\text{O}]$ .

4. What compounds are of use as accelerators in the vulcanization of rubber? Outline a method of preparing two such compounds. What economic advantages do you think would result from the use of accelerators in the rubber industry?

5. Write electronic formulas for the following classes of compounds: mercaptans, sulfones, sulfonic acids, sulfonamide ( $\text{RSO}_2\text{NH}_2$ ), trialkyl sulfonium salts.

6. Compare and contrast the basic and acidic properties of the alkyl derivatives of hydrogen sulfide, water and ammonia.

7. Prepare a table showing the similarity between the relation of thiocyanic acid to carbon disulfide, cyanamide to cyanic acid and carbon dioxide.

8. Outline methods of preparing the following: (a) butane sulfonic acid (2 methods); (b) dimethyl disulfide; (c) methyl isocyanate; (d) dimethyl sulfone; (e) sodium ethyl xanthate.

9. What would you predict would be the result of allowing  $\text{CH}_3\text{MgI}$  and carbon disulfide to interact? What properties would you predict for the product thus formed?

10.  $\beta$ -Disulfones,  $\text{RSO}_2\text{CH}_2\text{SO}_2\text{R}$ , like  $\beta$ -diketones,  $\text{RCOCH}_2\text{COR}$ , form sodium salts when treated with sodium methylate. Formulate the structures of the ion of the sodium salt. On the basis of electronic structure, can an enol form of  $\beta$ -disulfones be written? Explain.

11. Differentiate between (a)  $(\text{C}_2\text{H}_5\text{O})_2\text{SO}_2$  and  $\text{C}_2\text{H}_5\text{SO}_2\text{OC}_2\text{H}_5$ ; (b)  $\text{C}_4\text{H}_9\text{SH}$  and  $(\text{C}_2\text{H}_5)_2\text{S}$ .

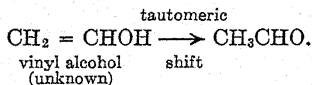
## CHAPTER XVI

### UNSATURATED ALCOHOLS, ACIDS, AND CARBONYL COMPOUNDS

The acids, alcohols, aldehydes, and ketones which have been considered in the previous chapters may be regarded as derivatives of the paraffin hydrocarbons. We shall now consider similar compounds which are derived from the unsaturated hydrocarbons. If the functional group (for example, the carboxyl group) is separated from the unsaturated linkage by two or more carbon atoms the two reactive portions of the molecule have little influence on each other. In such cases, the reactions of the compound are those characteristic of both the functional group, and an unsaturated hydrocarbon. If, however, the double linkage is within one or two carbon atoms of the functional group a number of peculiar properties often manifest themselves and give rise to special reactions. Examples of this will be noted particularly in the case of the unsaturated acids and carbonyl compounds.

#### UNSATURATED ALCOHOLS

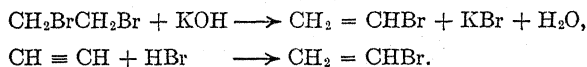
**Vinyl Alcohol.** The simplest imaginable unsaturated alcohol would be that formed by the replacement of one hydrogen atom of ethylene by a hydroxyl group. Such a compound is unknown, but we give to it the name vinyl alcohol. The reason for the non-existence of vinyl alcohol is evident from the discussion in Chap. XIII of the subject of tautomerism. Vinyl alcohol is the enol form of acetaldehyde; in all the reactions in which we would expect to obtain it, we find instead acetaldehyde itself:



We have already considered the problem of the existence of other enolic compounds which contain the grouping  $\text{C} = \text{COH}$  (p. 232).

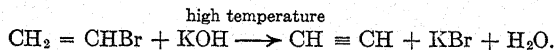
**Vinyl Halides and Esters.** Although vinyl alcohol can not be prepared, the corresponding halides and esters are stable substances. Vinyl bromide is formed by the action of strong po-

tassium hydroxide on ethylene dibromide or by the action of hydrogen bromide on acetylene:



**Vinyl chloride** can be prepared by similar reactions. Vinyl bromide is a sweet-smelling liquid which boils at 16°. It readily polymerizes under the action of light or certain catalysts, and forms an amorphous mass which is insoluble in all common solvents. In general, compounds containing the vinyl group,  $\text{CH}_2 = \text{CH}$ , are very prone to undergo polymerization and form compounds of high molecular weight. In this respect the vinyl compounds resemble the dienes (p. 76). The structure of the polymeric vinyl compound has not been established with certainty, but probably a long carbon chain is formed by the union of a number of molecules.

The halogen atom in the vinyl halides is extremely unreactive. In fact, all compounds containing a halogen atom attached to an unsaturated carbon atom ( $\text{C} = \text{CBr}$ ) differ greatly from the alkyl halides. For example, no reaction occurs when such substances are boiled with water or treated with cold alcoholic potassium hydroxide, sodium methylate, or potassium cyanide; all these reagents, it will be recalled, readily enter into metathetical reactions with the alkyl halides. It is usually possible to eliminate another molecule of hydrogen halide from the vinyl halides and similar compounds by the action of very strong alkali at a high temperature. In this way an acetylene linkage is formed:



The double linkage in vinyl bromide is very similar to the unsaturated linkage in ethylene itself. Thus, the vinyl compounds are readily oxidized and combine with bromine and hydrobromic acid. In the latter case the reaction takes place in such a way that the bromine goes to the carbon already containing the halogen atom, and ethylidene dibromide is the product:



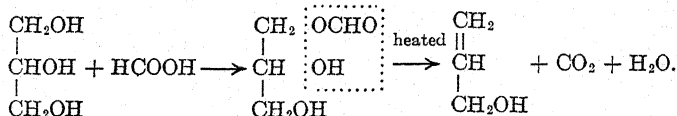
**Vinyl acetate**,  $\text{CH}_2 = \text{CHOCOCH}_3$ , has been prepared industrially from acetylene. Its polymers and those prepared from vinyl chloride are used in connection with the preparation of

artificial resins, varnishes, and lacquers. Polymeric vinyl acetate is known in the trade as "vinylite."

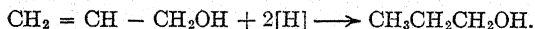
## SOME REPRESENTATIVE UNSATURATED ALCOHOLS

NAME	FORMULA	BOILING POINT	DENSITY AT 20°
Allyl alcohol	$\text{CH}_2 = \text{CHCH}_2\text{OH}$	97°	.854
Methyl-vinyl-carbinol	$\text{CH}_2 = \text{CHCHOHCH}_3$	96-97°	—
Allylcarbinol	$\text{CH}_2 = \text{CHCH}_2\text{CH}_2\text{OH}$	112-114°	.848
Vinyl-ethyl-carbinol	$\text{CH}_2 = \text{CHCHOHC}_2\text{H}_5$	114-115°	.840
Methyl-allyl-carbinol	$\text{CH}_2 = \text{CHCH}_2\text{CHOHCH}_3$	115°	.834
$\beta$ -Allyl-ethyl alcohol	$\text{CH}_2 = \text{CHCH}_2\text{CH}_2\text{CH}_2\text{OH}$	139°	.863

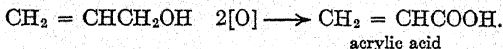
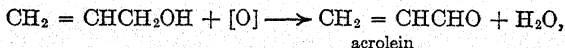
**Allyl Alcohol.** The simplest compound in which the hydroxyl group is not directly attached to the double linkage, but on the next carbon atom, is allyl alcohol,  $\text{CH}_2 = \text{CHCH}_2\text{OH}$ . It is evident that this compound is not an enol, and therefore does not tautomerize to a ketone or aldehyde. Allyl alcohol is best prepared by heating glycerol with oxalic acid or formic acid. With the latter, glycerol formate is first formed, which then decomposes on further heating to yield allyl alcohol:



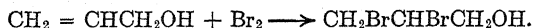
The structure of allyl alcohol is established by the fact that on reduction it combines with two hydrogen atoms, yielding normal propyl alcohol:



This fact proves that the compound has either the structure given above or  $\text{CH}_3\text{CH} = \text{CHOH}$ . The latter possibility is excluded since allyl alcohol can be shown to be a primary alcohol. Thus, it is oxidized to an aldehyde which, in turn, is oxidized to an acid (the yields in these reactions are poor, however):

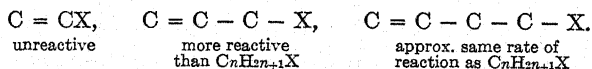


Allyl alcohol forms esters with acids in the usual manner. The ethylenic double linkage also has the usual capacity to combine with a number of other atoms or groups. The addition of hydrogen has been mentioned; it readily combines with bromine:



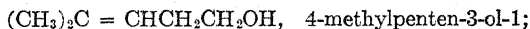
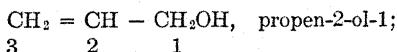
Allyl alcohol is a liquid of irritating odor which is miscible with water in all proportions. It boils at 97°.

**Allyl Halides.** Allyl bromide, allyl iodide, and allyl chloride can be prepared from allyl alcohol by the use of the phosphorus halides or by the action of the halogen acids. The allyl halides are extremely reactive and enter into all the double decomposition reactions characteristic of the alkyl halides. Indeed, such reactions are much more rapid than in the case of the alkyl halides. For example, in the alkylation of sodium acetoacetic ester, allyl iodide is four times as rapid in its action as methyl iodide and 400 times as fast as isopropyl iodide. In the double decomposition reaction with potassium iodide, which yields the corresponding iodo compounds, allyl chloride is 80 times as reactive as normal butyl chloride. It is very interesting that a double linkage *immediately adjacent* to the carbon atom which holds the halogen has increased the speed of the metathetical reactions. In the case of the vinyl compounds where the halogen is *directly attached* to the unsaturated carbon atom metathetical reactions are so slow as to be inappreciable. These facts illustrate the great influence which a carbon-carbon double bond has on a nearby functional group or reactive atom. In those unsaturated halides in which the double bond is two or more carbons removed from the halogen atom, there is very little, if any, increase or decrease in the speed of the metathetical reactions:



**Allyl Derivatives in Nature.** A number of derivatives of allyl alcohol are found in nature. Allyl sulfide,  $(\text{C}_3\text{H}_5)_2\text{S}$  (p. 266), is the chief constituent of oil of garlic, and allyl isothiocyanate,  $\text{C}_3\text{H}_5\text{NCS}$  (p. 272) (mustard oil), occurs in the mustard seed in combination with glucose (*i.e.*, as a glucoside).

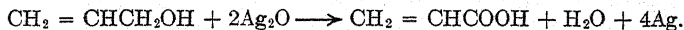
**Nomenclature of Unsaturated Alcohols.** The unsaturated alcohols are readily named by the Geneva system. The numbering is chosen so that the carbon atom bearing the hydroxyl group has the smallest number; as usual, the longest possible chain of carbon atoms is the basis of the name. The following examples will make the method evident:



### UNSATURATED ACIDS

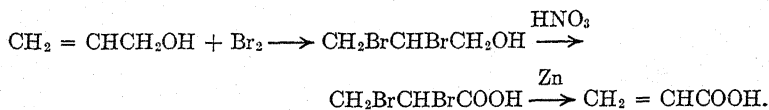
The acids which are derived from the unsaturated hydrocarbons are usually classified according to whether an ethylenic or acetylenic group is present and with regard to the relative position of the carboxyl group. For example, acids which are related to the olefin hydrocarbons and have the general formula  $\text{C}_n\text{H}_{2n-1}\text{COOH}$ , may be either  $\alpha$ ,  $\beta$ -unsaturated acids, in which the double bond is adjacent to the carboxyl group,  $\text{RCH} = \text{CHCOOH}$ ;  $\beta$ ,  $\gamma$ -unsaturated acids,  $\text{RCH} = \text{CHCH}_2\text{COOH}$ ;  $\gamma$ ,  $\delta$ -unsaturated acids, etc. Where the double bond is two or more atoms removed from the carboxyl group, generally it seems to be without influence on the latter, and the reactions of the molecule can be readily predicted. Such acids are the unsaturated acids which have been considered in a previous chapter in connection with the fats (p. 183). We shall now consider a few  $\alpha$ ,  $\beta$ -unsaturated acids which are prepared by special methods and which have some characteristic properties.

**Acrylic Acid.** The acid obtained by oxidizing allyl alcohol is acrylic acid. It is the simplest  $\alpha$ ,  $\beta$ -unsaturated acid:

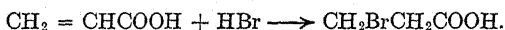
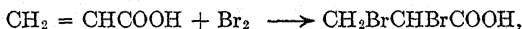
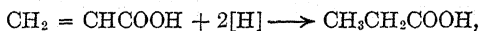


Since the double linkage in allyl alcohol is attacked by a number of oxidizing agents, rather special reagents as silver oxide must be employed. A cheaper and more convenient method of preparing acrylic acid is first to form the dibromide,  $\text{CH}_2\text{BrCHBrCH}_2\text{OH}$ , next oxidize this to the corresponding acid (a reaction which can be carried out with a number of powerful agents, since there is no double bond to interfere), and finally, to remove the two bromine atoms by the action of zinc. This last reaction

is exactly analogous to one used in the preparation of ethylene:



Acrylic acid is a liquid which boils at 141° and solidifies at 12°. It is a slightly stronger acid than acetic acid (the influence of the adjacent double linkage being manifest). It enters into all the reactions characteristic of the organic acids. The double linkage manifests itself by the fact that the acrylic acid combines with nascent hydrogen, bromine, and hydrobromic acid:

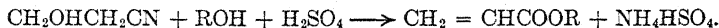


The first reaction serves to establish the structure of acrylic acid, since the reduction product, propionic acid, is a substance of known structure. Not only can this reduction be accomplished catalytically, but it may also be done by the use of sodium amalgam. This fact is of particular interest as ethylene is not affected by sodium amalgam. The reaction with hydrobromic acid has been already mentioned (p. 208). It was noted that the bromine attached itself to the  $\beta$ -carbon atom (furthest from the carboxyl group), although this carbon carries more hydrogen than the other. This is contrary to the Markownikoff rule (p. 65) which in this instance would predict that the bromine would go to the  $\alpha$ -carbon atom since it holds the least hydrogen. It will be recalled that when Markownikoff's rule was discussed, it was emphasized that it applied only to the unsaturated hydrocarbons. *With  $\alpha$ ,  $\beta$ -unsaturated acids, the halogen atom always unites with the beta carbon atom.* A probable explanation of this mode of addition of the hydrogen halides to the  $\alpha$ ,  $\beta$ -unsaturated acids will be discussed in connection with the reactions of the unsaturated aldehydes and ketones (p. 293).

**Acrylic Esters.** Acrylic esters and  $\alpha$ -methyl acrylic esters,  $\text{CH}_2 = \text{C}(\text{CH}_3)\text{COOR}$ , deserve special mention since they are readily polymerized by light, heat, and peroxides. By carefully controlling this reaction, clear, colorless resins are obtained which are known as "acryloids." These resins have excellent optical

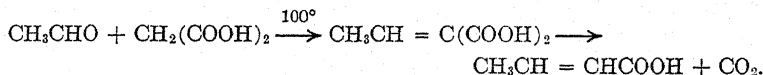
properties and can be molded into lenses, prisms, and sheets which are used to make laminated safety glass.

Industrially, acrylic ester is prepared from ethylene chlorohydrin which, as we have seen (p. 64), is readily available from petroleum.



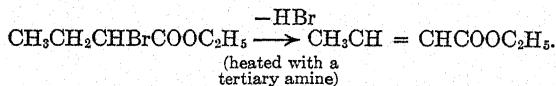
Acrylic esters having a methyl group,  $\text{CH}_2 = \text{C}(\text{CH}_3)\text{COOR}$ , in the alpha position are made from acetone cyanohydrin (acetone and hydrogen cyanide) by the same steps outlined above.

**The Crotonic Acids.** Crotonic acid,  $\text{CH}_3\text{CH} = \text{CHCOOH}$ , is another  $\alpha$ ,  $\beta$ -unsaturated acid. It is very similar in its chemical properties to acrylic acid. It may be prepared by methods outlined above for the preparation of  $\alpha$ ,  $\beta$ -unsaturated acids and, in addition, by a convenient reaction from acetaldehyde. Acetaldehyde and malonic acid, when heated in glacial acetic acid solution at  $100^\circ$ , condense to form an unsaturated dibasic acid, which at this temperature loses carbon dioxide, forming crotonic acid:



Similar condensation reactions between other aldehydes and malonic acid offer a convenient method of preparing  $\alpha$ ,  $\beta$ -unsaturated acids, ( $\text{RCH} = \text{CHCOOH}$ ), from aldehydes.

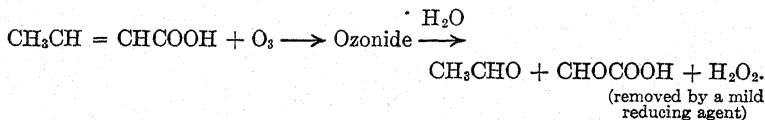
**Other Methods of Preparing  $\alpha$ ,  $\beta$ -Unsaturated Acids.** Still another method of preparing  $\alpha$ ,  $\beta$ -unsaturated acids is illustrated by the method often used for preparing crotonic acid. This consists in heating the ester of  $\alpha$ -bromobutyric acid with a tertiary amine (diethylaniline,  $\text{C}_6\text{H}_5\text{N}(\text{C}_2\text{H}_5)_2$ ). It is a difficult matter to eliminate hydrobromic acid from an  $\alpha$ -bromo acid (as contrasted to a  $\beta$ -bromo acid), but the process can be carried out if the esters are employed:



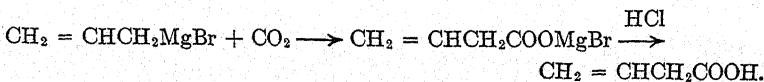
$\alpha$ ,  $\beta$ -Unsaturated acids cannot be prepared from  $\alpha$ -hydroxy acids, such as lactic acid, because under the conditions of dehydration lactides result (p. 213). However, it is possible to dehydrate the corresponding nitriles and in certain instances the corresponding esters. On the other hand,  $\beta$ -hydroxy acids, which can be prepared by the Reformatsky reaction (p. 210), are generally

dehydrated by strong acids to  $\alpha$ ,  $\beta$ -unsaturated acids. This constitutes another general method of preparing this class of substances.

**Isomeric Crotonic Acids.** Crotonic acid occurs in two isomeric forms. The explanation of this isomerism will be considered shortly. Crotonic acid itself is a crystalline solid melting at  $72^\circ$  and boiling at  $189^\circ$ . It is fairly soluble in water. The isomer, **isocrotonic acid**, melts at  $15.5^\circ$  and boils at  $169^\circ$ . On heating the isocrotonic acid to  $100^\circ$ , it partly rearranges into the higher melting isomer. The rearrangement is accelerated by traces of iodine or acid or by exposure of a solution of isocrotonic acid to sunlight. In their chemical behavior these two acids are identical, and the same structural formula must be assigned to them. Both are readily reduced by the action of sodium amalgam or by catalytic hydrogenation to *n*-butyric acid. This fact establishes the carbon skeleton, and only the position of the double linkage remains in question. Both acids combine with hydrogen iodide to give the same beta iodobutyric acid. Ozonization followed by decomposition of the ozonides transforms *both* acids into a mixture of acetaldehyde and glyoxylic acid. This is conclusive evidence that crotonic and isocrotonic acids both must be represented by the structural formula  $\text{CH}_3\text{CH} = \text{CHCOOH}$ .

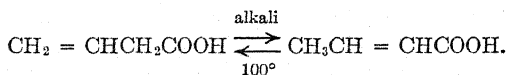


**Vinylacetic Acid.** The simplest  $\beta$ ,  $\gamma$ -unsaturated acid is vinylacetic acid,  $\text{CH}_2 = \text{CHCH}_2\text{COOH}$ . It can be obtained by treating the Grignard reagent formed from allyl bromide with carbon dioxide. There is great difficulty in the preparation of the Grignard reagent from the allyl halides, since they are prone to undergo the Wurtz reaction (p. 42) when treated with magnesium, forming a compound known as diallyl,  $\text{CH}_2 = \text{CHCH}_2\text{CH}_2\text{CH} = \text{CH}_2$ . This fact again illustrates the enhanced reactivity of allyl halides.

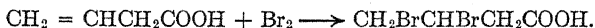


Vinylacetic acid rearranges into the isomeric crotonic acid when

it is boiled with alkali; this reaction is reversible and proceeds to a definite equilibrium:

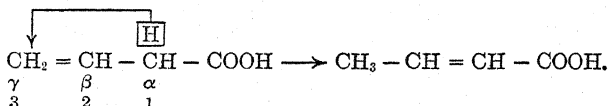


It is reduced to butyric acid and combines with bromine to yield  $\beta$ ,  $\gamma$ -dibromobutyric acid:

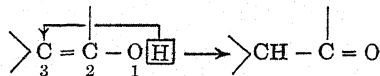


Because of the easy transformation of vinylacetic acid into crotonic acid, it is *not* prepared by hydrolysis of the corresponding nitrile. This nitrile is readily prepared by the action of potassium cyanide on the allyl halides, and is known as allyl cyanide,  $\text{CH}_2 = \text{CH} - \text{CH}_2\text{CN}$ . On hydrolyzing this nitrile with alkali, crotonic acid is formed, because the vinylacetic acid first produced rearranges under the influence of the alkali.

It is interesting to note that the shift of the double linkage involved in the change from vinylacetic acid to crotonic acid involves a shift of the hydrogen atom from the  $\alpha$  carbon atom to the  $\gamma$  carbon atom:



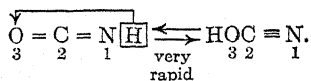
This shift through a three-atom system is similar to the shift of a hydrogen atom involved in the change from an enol to a ketone:



In the case of the three-carbon system (no oxygen atom is involved), such a shift occurs only slowly even under the influence of such reagents as boiling sodium hydroxide; on the other hand, the speed of enolization and ketonization is very great even in the presence of but a trace of catalyst. The three-atom system containing an oxygen atom is more *mobile* than the carbon system. In both systems, however, we are dealing with a truly reversible reaction. Although in the case of crotonic acid, the  $\alpha$ ,  $\beta$  form is present at equilibrium to the extent of 98 per cent, with certain alkyl derivations the  $\beta$ ,  $\gamma$  form predominates in the equilibrium mixture.

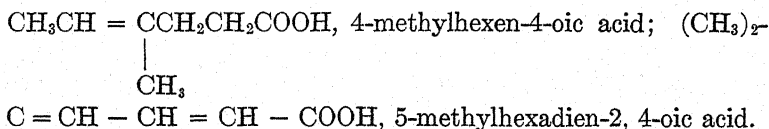
An unsaturated three-atom system is present in cyanic acid (p. 253), but it contains a nitrogen atom also. One is tempted to postulate that in this case the mobility is so great that no catalyst is needed and the tautomers

(isomers) can not be isolated; this explanation accords well with the behavior of cyanic acid:

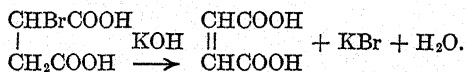


**Nomenclature of Unsaturated Acids.** Unsaturated acids can be named by a variety of procedures. The position of the double bond may be indicated by Greek letters, and the symbol  $\Delta$ . Thus, crotonic acid,  $\text{CH}_3\text{CH}=\text{CHCOOH}$ , is butenoic acid  $\Delta^{\alpha,\beta}$ , while vinylacetic acid,  $\text{CH}_2=\text{CHCH}_2\text{COOH}$ , is butenoic acid  $\Delta^{\beta,\gamma}$ . The unsaturated hydrocarbon, in this case butene, is the basis for the name which should correspond to the longest carbon chain.

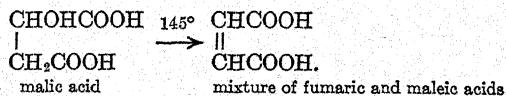
According to the Geneva system, the position of the double bond is indicated by a number placed in the name immediately after the "en"; the numbering always starts with the carbon atom of the carboxyl group. Thus,  $\text{CH}_3\text{CH}=\text{CHCOOH}$  is called buten-2-oic acid and  $\text{CH}_2=\text{CHCH}_2\text{COOH}$  is buten-3-oic acid. As an application of the Geneva system to complicated unsaturated acids, the following examples may be cited:



**Fumaric and Maleic Acids.** These two isomeric unsaturated dibasic acids are of the greatest interest and importance. They are both represented by the same structural formula  $\text{HOOCCH}=\text{CHCOOH}$ . Fumaric acid occurs widely distributed in nature and is found in small quantities in many plants. It may be prepared by the action of alkali on bromosuccinic acid (which is obtained by brominating succinic acid):



It is also formed by heating *malic acid* ( $\alpha$ -hydroxy succinic acid) (p. 216).

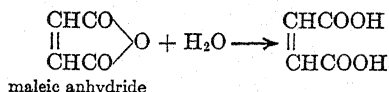


Maleic anhydride and fumaric acid are prepared industrially by the *catalytic oxidation of benzene*,  $C_6H_6$  (p. 388), by air at 400°–500°. The properties of fumaric and maleic acids are given below in the following table:

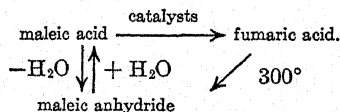
PHYSICAL PROPERTIES OF MALEIC AND FUMARIC ACIDS

	MELTING POINT	SOLUBILITY IN 100 CC. $H_2O$ AT 18°	$K_A$ (18°)	HEAT OF COMBUSTION (KG. CAL.)
Maleic acid	130°	very soluble	$13 \times 10^{-3}$	326.9
Fumaric acid	287°	.445	$1.1 \times 10^{-3}$	320.1

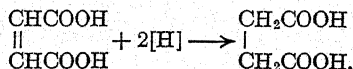
The two acids differ strikingly in their physical properties and in their tendency to lose water. Maleic acid readily forms an anhydride when heated by itself or in the presence of a dehydrating agent. Fumaric acid does not form an anhydride, but when it is heated to a very high temperature maleic anhydride is formed. **Maleic anhydride** on treating with water slowly yields maleic acid:



Maleic acid is readily converted into fumaric acid by the catalytic action of warm acids, halogens, or sunlight. This change is accompanied by the evolution of heat (*i.e.*, is exothermic), as is evident from the differences in the heats of combustion of the two acids. Maleic acid is richer in energy than fumaric by about 6 kg. cal. The following diagram illustrates the relationship of the two isomers:

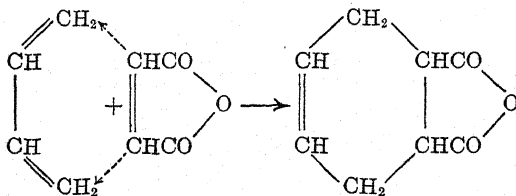


The structures of maleic and fumaric acids are readily established by the fact that on reduction both yield succinic acid:



Both maleic and fumaric acids combine with hydrobromic acid to give the same bromosuccinic acid, and both can be converted into malic acid by heating with water and a catalyst. They are oxidized by permanganate and combine with bromine, though the latter reaction is much slower than with most derivatives of ethylene.

**Reaction of Maleic Anhydride with Dienes.** Maleic anhydride readily combines with 1, 3 dienes (p. 73) to give a ring compound. The reaction with butadiene, for example, is as follows:



This reaction is general for the system  $C = C - C = C$  and is often used to determine whether a new compound has a conjugated system of double bonds. It is a striking demonstration of the capacity of a conjugated system to combine in the 1, 4 position (p. 73). Certain other substances which contain an ethylene bond adjacent to a carbonyl group also can add to 1, 3 diene systems. Reactions of this type are known as **diene syntheses**.

#### GEOMETRICAL ISOMERISM

We have seen that there are two crotonic acids, both of which have the same structural formula, and that maleic and fumaric acids are another pair of isomers whose existence can not be explained in terms of the simple structural theory. In these instances we are not dealing with optical isomers since none of these compounds are optically active, and there are no asymmetrical carbon atoms in the molecule. With the aid of the tetrahedral model of a carbon atom, however, a very satisfactory explanation of the isomerism of these unsaturated compounds can be formulated. A double linkage must be represented with the models by the union of two tetrahedra along one edge. This is shown in the accompanying diagrams. It is clear from an inspection of these diagrams (or better by handling the models themselves) that it is not possible for the two carbon atoms which are joined by a double bond to rotate freely about each other. The double bond

is a rigid union of the two atoms. If now the two carbon atoms involved in the double bond carry two different groups, two arrangements are possible depending on whether certain groups are over each other or away from each other. These two spatial ar-

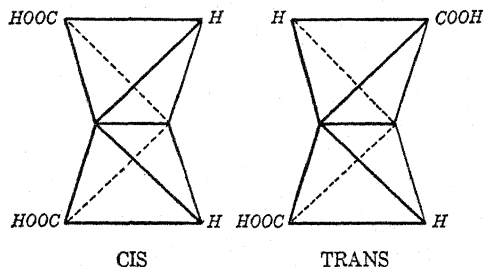
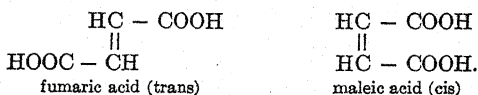


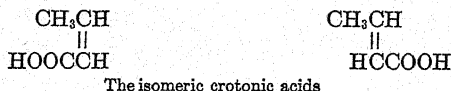
Fig. 24. Diagrams of models of maleic and fumaric acids.

rangements correspond to the two isomers. Thus, maleic acid and fumaric acid are represented by the models shown in Fig. 24. They are represented in a plane as follows:

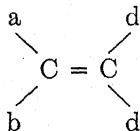


The names "cis" and "trans" are applied to the isomers to denote whether the similar groups are over each other or in the opposite configuration. Such isomers are called *geometrical isomers*. Clearly geometrical isomerism is a branch of stereoisomerism.

The fact that maleic acid readily forms an anhydride is taken as evidence that it corresponds to the *cis* form. The construction of models shows that two carboxyl groups adjacent to each other in space could readily lose water to form a cyclic anhydride. On the other hand, the two carboxyl groups which are in the *trans* position could not. In the case of the isomeric crotonic acids it has not been possible, as yet, to determine definitely which isomer is *cis* and which *trans*. There is in this case no simple reaction such as anhydride formation to serve as an indicator of the configuration:



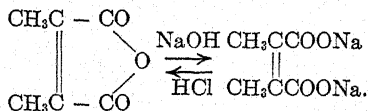
In general, it is evident that geometrical isomers may be expected only if both unsaturated carbon atoms carry two different atoms or groups. Thus, compounds of the general type



will not have geometrical isomers since the two groups on one carbon atom are the same, and two different spatial arrangements are not possible.

This isomerism of unsaturated compounds, as we have seen, is due to a restricted rotation of two carbon atoms joined by a double bond. On the other hand, two carbon atoms are free to rotate around a single bond. If this were not so, isomers would be found with such saturated compounds as succinic acid. It is a remarkable fact that the simple assumption, that there is free rotation where the models show it to be possible and restricted rotation where they show it to be impossible, corresponds to the actual experimental facts. Modern physics has thrown some light on the nature of the electrical forces involved in the carbon-carbon bond, and has completely verified the picture of the fundamental difference between a single and a multiple linkage. By studying X-ray diffraction of crystals and electron diffraction of gases, it has been found that the distances between atomic centers is for C—C, 1.54Å; for C=C, 1.34Å; for C≡C, 1.20Å. The shortening of the distance between the atoms corresponds to a greater binding force and along with this comes also restricted rotation, as the existence of geometrical isomers demonstrates. On the other hand, the conversion of one geometrical isomer into the other (*e.g.*, maleic to fumaric) shows that the restriction on the rotation may be overcome. This isomerization may be imagined as being the opening of one linkage of the two bonds followed by rotation of the atoms around the remaining bond.

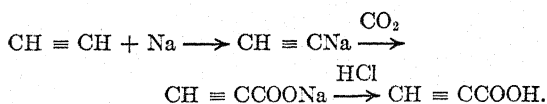
**Anhydride of Dimethyl Maleic Acid.** Dimethyl maleic acid,  $\text{HOOC}(\text{CH}_3) = \text{C}(\text{CH}_3)\text{COOH}$ , is a very interesting compound because of the fact that it so readily forms the anhydride that the *free acid is unknown*. The esters and salts of the acid may be prepared, but when one attempts to separate the free acid by acidifying an aqueous solution of the disodium salt, the anhydride spontaneously forms even in an aqueous solution. This anhydride dissolves in sodium hydroxide with the formation of the disodium salt:



Dimethyl fumaric acid, like fumaric acid itself, does not form an anhydride.

**Acetylenic Compounds.** If a model is made of the acetylenic linkage it is clear that no isomers would be predicted. This is illustrated in Fig. 25. Such a prediction is in entire accord with

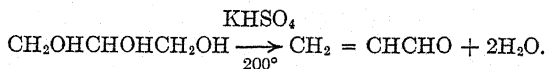
the experimental facts. Propiolic acid,  $\text{CH} \equiv \text{CCOOH}$ , which can be prepared from sodium acetylene and carbon dioxide, exists in only one form:



The same is true of other acetylene compounds.

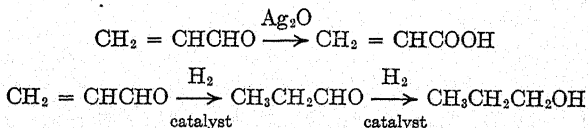
#### UNSATURATED ALDEHYDES AND KETONES

**Acrolein.** The simplest unsaturated aldehyde is acrolein or acrylic aldehyde,  $\text{CH}_2 = \text{CHCHO}$ . It is a colorless liquid (b.p.  $57^\circ$ ) with an extremely powerful and irritating odor. It may be formed by the careful oxidation of allyl alcohol, but is usually prepared by the dehydration of glycerol. This can be done by heating glycerol with potassium acid sulfate; the unsaturated aldehyde being volatile, is collected as a distillate:



Acrolein is formed in small amounts when glycerides (fats) are heated to a high temperature. The irritating vapors of acrolein are sometimes noticed when fats are heated or burned.

Acrolein gives the reactions of both aldehydes and olefins. As an aldehyde it can be oxidized to the corresponding acid (it reduces ammoniacal silver nitrate); it reacts with the Grignard reagent to give the corresponding unsaturated alcohol. The presence of the ethylene linkage is demonstrated by the fact that the compound adds bromine to form a dibromide and further by the hydrogenation (in the presence of platinum catalyst) to propionaldehyde:



If the hydrogenation is stopped after one mole of hydrogen is ab-

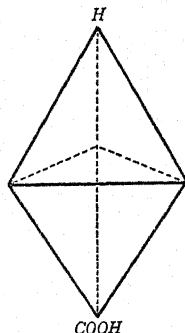


Fig. 25. Diagram of model of propiolic acid.

sorbed, the product is predominantly propionaldehyde. On further reduction, propyl alcohol is obtained.

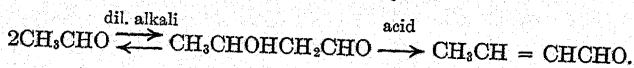
The structure of acrolein follows from these various reactions which serve to demonstrate (1) the presence of an aldehyde group; (2) a three-carbon chain; and (3) the presence of a double linkage.

PHYSICAL PROPERTIES OF SOME UNSATURATED ALDEHYDES

NAME	FORMULA	BOILING POINT	DENSITY AT 20°	SOLUBILITY GRAMS PER 100 GRAMS OF WATER
Acrolein	$\text{CH}_2=\text{CHCHO}$	52.5°	.841	about 40
Crotonaldehyde	$\text{CH}_3\text{CH}=\text{CHCHO}$	104.5°	.847	—
$\alpha, \beta$ -Dimethylacrolein	$\text{CH}_3\text{CH}:\text{CCHO}$   $\text{CH}_3$	115–119°	.87	2
$\alpha$ -Methyl- $\beta$ -ethylacrolein	$\text{C}_2\text{H}_5\text{CH}=\text{CCHO}$   $\text{CH}_3$	137°	.857	very small

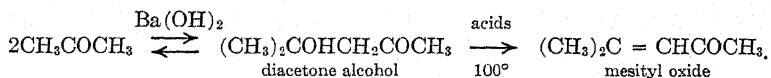
**Polymerization of Acrolein.** Like many other substances containing the vinyl group ( $\text{CH}_2 = \text{CH} -$ ), acrolein readily polymerizes forming substances of high molecular weight. This polymerization takes place so readily in the case of acrolein that it is very difficult to store the material unless certain substances are added as stabilizers. The polymerization of acrolein and other unsaturated substances is usually catalyzed by the presence of small amounts of peroxide, which are slowly formed by the action of the oxygen of the air. Substances which will react with the peroxides and destroy them prevent the polymerization. Such substances are the antioxidants, which we have mentioned in connection with the stabilizing of gasoline (p. 55).

**Crotonaldehyde.** Crotonaldehyde or crotonic aldehyde,  $\text{CH}_3\text{CH} = \text{CHCHO}$ , is the next higher homolog in the series of  $\alpha, \beta$ -unsaturated aldehydes. It is readily prepared from acetaldehyde through the aldol condensation (p. 117). When aldol is heated with dilute acids or certain other catalysts it readily loses a molecule of water, forming crotonaldehyde.



Crotonaldehyde is a liquid which boils at 105°. Its reactions are very similar to those of acrolein, except that it can not be polymerized.

**Alpha, Beta-Unsaturated Ketones.** A great number of  $\alpha$ ,  $\beta$ -unsaturated ketones are known since they may be readily prepared by the condensation of ketones and aldehydes. One of the simplest is **mesityl oxide**. It is formed by heating diacetone alcohol (p. 118) with a trace of acid or iodine. These reagents cause an almost quantitative dehydration of the hydroxy ketone with the formation of an unsaturated ketone:

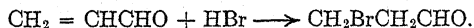


It is also possible to obtain mesityl oxide directly from acetone by the action of acids; the yields are very poor, however. Undoubtedly in this reaction diacetone alcohol is first formed which then undergoes dehydration. When this method of preparing mesityl oxide is used, another unsaturated ketone, **phorone**,  $(\text{CH}_3)_2\text{C}=\text{CHCOCH}=\text{C}(\text{CH}_3)_2$ , is also formed. Mesityl oxide is a colorless liquid with a peppermint odor. Phorone is a solid which melts at 28°. The boiling points of these and certain other unsaturated ketones are given in the table. Both these compounds on boiling with dilute alkali undergo cleavage with the regeneration of acetone. This is the reversal of the method by which they are formed. Undoubtedly the first step is the addition of water to the unsaturated linkage (or linkages) and the formation of the hydroxyl compound which then undergoes the reversal of the aldol condensation forming acetone.

PHYSICAL PROPERTIES OF SOME UNSATURATED KETONES

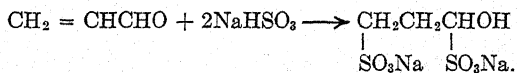
NAME	FORMULA	BOILING POINT	DENSITY AT 20°
Methyl vinyl ketone	$\text{CH}_2=\text{CHCOCH}_3$	80°	.864
Ethyl vinyl ketone	$\text{CH}_2=\text{CHCOC}_2\text{H}_5$	38°	
Ethylidene acetone	$\text{CH}_3\text{COCH}=\text{CHCH}_3$	(68 mm.)	.862
Allylacetone	$\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{COCH}_3$	125-128°	
Mesityl oxide	$(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$	129°	.865
Phorone	$(\text{CH}_3)_2\text{C}=\text{CHCOCH}=\text{C}(\text{CH}_3)_2$	130°	
		200°	.885

**Characteristic Reactions of  $\alpha$ ,  $\beta$ -Unsaturated Carbonyl Compounds.** The  $\alpha$ ,  $\beta$ -unsaturated aldehydes and ketones, since they contain a double bond immediately adjacent to the carbonyl group, have a number of special reactions. These could not be predicted from a knowledge of the characteristics of the carbon-carbon double bond and the carbon-oxygen double linkage. As the first example of the peculiar reactions, we may mention the fact that all  $\alpha$ ,  $\beta$ -unsaturated ketones and aldehydes combine with halogen acids in such a way that the halogen atom attaches itself to the beta carbon atom. For example, acrolein combines with hydrogen bromide as follows:

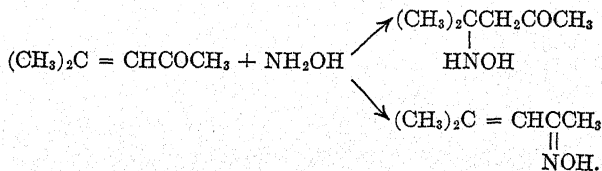


(A similar situation was encountered with the  $\alpha$ ,  $\beta$ -unsaturated acids and is also true of their esters.)

A much more striking peculiarity of  $\alpha$ ,  $\beta$ -unsaturated aldehydes and ketones is the fact that the carbon double linkage appears to combine with reagents which would be expected to attack only the carbonyl group. For example, when acrolein is treated with sodium bisulfite two moles of the reagent add to the substance, one going normally to the carbonyl group and the other combining with the ethylene linkage:

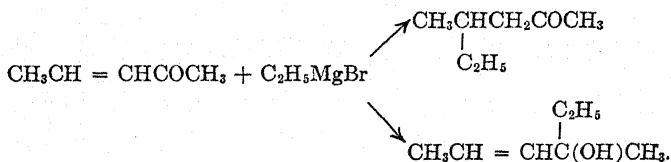


Hydrocyanic acid and hydroxylamine also often combine with the ethylenic linkage of  $\alpha$ ,  $\beta$ -unsaturated ketones and aldehydes. The reaction between mesityl oxide and hydroxylamine may be used as an illustration. When these two substances are allowed to interact at room temperature two different products are formed; one of these is the normal oxime and the other is the compound formed by addition of the hydroxylamine to the ethylenic linkage:



The reaction between the Grignard reagent and  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds also may take an abnormal course.

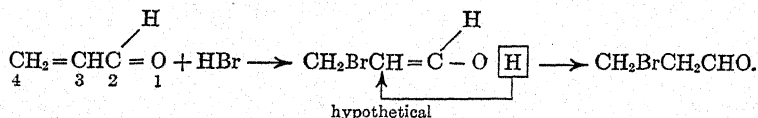
For example, the action of ethyl magnesium bromide on ethylidene acetone gives the two following products:



In one of these cases the Grignard reagent has apparently added to the carbon-carbon double linkage. It should be noted that such reagents as hydrocyanic acid, hydroxylamine, sodium bisulfite, and the Grignard reagent do not add to ethylenic hydrocarbons, nor do they add to the carbon double linkage in unsaturated aldehydes or ketones *unless this linkage is in the  $\alpha, \beta$  position*.

**Conjugated Systems of Double Bonds.** Two explanations have been offered for the peculiar reactions of  $\alpha, \beta$ -unsaturated carbonyl compounds. On the one hand, it may be said that the carbon-carbon double bond has been made more active by the presence of the adjacent carbonyl group and will therefore combine with a number of reagents for which it otherwise has no affinity. The two carbon atoms of the double bond are under different influences and the reagent always adds in such a manner that the hydrogen atom attaches itself to the carbon immediately adjacent to the carbonyl group.

An entirely different explanation was offered by Johannes Thiele<sup>1</sup> in 1899, and is supported by a number of experimental facts. He supposed that the actual addition took place in such a way that the hydrogen atom of the reagent combined with the oxygen, and the rest of the reagent combined with the carbon atom. The first product then tautomerized to the final ketone or aldehyde. This mechanism may be illustrated by the addition of hydrobromic acid to acrolein as follows:

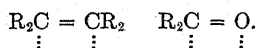


It will be recognized that in the first step of this mechanism a reaction is involved analogous to the 1, 4 addition of the dienes

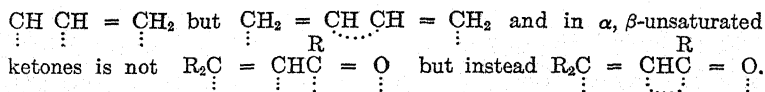
<sup>1</sup> Johannes Thiele (1865-1918). Professor at the University of Strassburg.

(p. 73). In only a few cases has it been possible to prove that 1, 4 addition takes place with  $\alpha$ ,  $\beta$ -unsaturated ketones and with aldehydes. In addition of the Grignard reagent, it has been shown that the magnesium atom is actually attached to the oxygen as required by the theory of 1, 4 addition. Arguing by analogy from such facts, many chemists believe that all the characteristic reactions of  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds proceed by 1, 4 addition.

**Thiele's Theory of Partial Valence.** As an explanation of the phenomenon of 1, 4 addition, Thiele advanced his theory of Partial Valences. Although this theory is certainly far from satisfactory, it gives a picture of one possible mode of addition to conjugated systems. It may be represented by the following diagram in which the dotted lines represent what Thiele called "partial valences," a concept for which it is difficult to form a satisfactory physical picture. In a normal double linkage the partial valences are free and serve to attract the usual reagents:



In a conjugated system, however, the adjacent partial valences are mutually satisfied, and the free partial valences only occur at the ends of the system (1, 4 positions); thus, the conjugated system in butadiene is not  $\text{CH}_2 =$

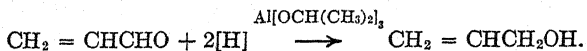


Additions therefore occur in the 1, 4 position.

It must be emphasized that while conjugated systems have the possibility of 1, 4 addition and often manifest this possibility, they also take part in many reactions in which each individual double linkage reacts in a normal way. Such reactions are often spoken of as 1, 2 additions. For example, the combination of acrolein with bromine is such a reaction, and the formation of the normal oxime proceeds in the same fashion. Thiele's theory of partial valence appears to predict that such 1, 2 additions would *not* occur.

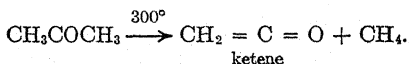
**Reduction of Unsaturated Carbonyl Compounds.** We have seen that when  $\alpha$ ,  $\beta$ -unsaturated aldehydes and ketones are reduced, it is the double bond adjacent to the carbonyl group which is reduced first. This occurs during catalytic hydrogenation and even with such reagents as sodium and aluminum amalgam which ordinarily do not effect an ethylene bond. Probably this is due to a 1, 4 addition at the ends of the conjugated system. Because of this fact, the reduction of the carbonyl group in  $\alpha$ ,  $\beta$ -unsaturated

aldehydes and ketones can not be accomplished by the usual methods. For this type of reaction, aluminum isopropylate (p. 115) serves admirably; thus acrolein can be converted into allyl alcohol according to the following reaction:

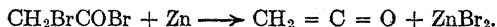


### KETENES

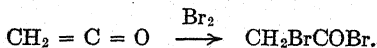
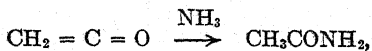
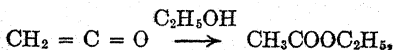
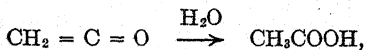
A group of substances known as the ketenes may be considered as a special class of unsaturated ketones. Their structure contains the linkage  $\text{C} = \text{C} = \text{O}$ , and they manifest such peculiar reactions that they are usually considered as a class by themselves. The simplest member of the class is ketene itself. It is formed by passing acetone through a hot tube:



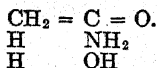
It can also be prepared by treating bromoacetyl bromide with zinc dust. This is a general method of preparing ketenes:



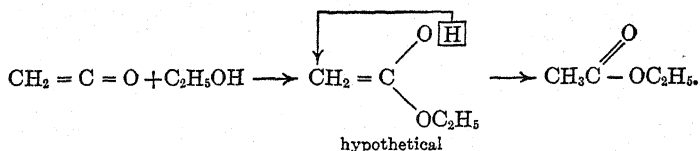
**Ketene** is a colorless gas, quite poisonous, with a characteristic, extremely unpleasant odor. It liquefies at  $-56^\circ$ . Like all the representatives of this class, it is extremely reactive, combining with a great variety of reagents. Some of these addition reactions of ketene are illustrated by the following equations:



With the exception of the last reaction it will be noted that the reaction of ketene may be regarded as the addition of a hydrogen atom to the  $\text{CH}_2$  group and a residue to the highly unsaturated central carbon atom. Thus, for example:



All these processes probably involve a mechanism in which the first reaction involves only the carbonyl group, and is followed by a tautomerization of the enolic compound first formed. This mechanism has been proved in at least one instance. It may be illustrated by the case of the action of alcohol on ketene:



The ketenes are classified into aldoketenes, having the general formula  $\text{RCH} = \text{C} = \text{O}$ , and ketoketenes,  $\text{R}_2\text{C} = \text{C} = \text{O}$ . Aldoketenes polymerize to dimolecular compounds so readily that it is very difficult to work with them.

### QUESTIONS AND PROBLEMS

1. Write equations for the following reactions: (a) glycerol and oxalic acid (heated); (b) ethyl crotonate +  $\text{HBr}$ ; (c)  $\text{C}_6\text{H}_7\text{CHO} + \text{CH}_2(\text{COOH})_2$  (heated); (d)  $\text{CH}_2 = \text{CHCH}_2\text{CN}$  boiled with  $\text{NaOH}$ ; (e)  $(\text{CH}_3)_2\text{C} = \text{CHCOCH}_3 + \text{NaHSO}_3$ ; (f)  $\text{C}_2\text{H}_5\text{CH} = \text{C} = \text{O} + \text{C}_4\text{H}_9\text{OH}$ .

2. What is meant by a conjugated system of double bonds? In what ways are such systems peculiar? Discuss briefly Thiele's theory of partial valence, including a discussion of its limitations. On the basis of this theory predict the products resulting from the following reactions:

(a) isoprene +  $\text{HBr}$ ; (b)  $\text{CH}_3\text{CH} = \text{CHCHO} + \text{NaHSO}_3$ ; (c)  $(\text{CH}_3)_2\text{C} = \text{CHCOC}_2\text{H}_5 + \text{CH}_3\text{MgI}$  followed by hydrolysis.

3. Discuss briefly the isomerism of fumaric and maleic acid. How does this isomerism differ from optical isomerism? Why is it difficult to determine the configurations of the two crotonic acids? What conclusion is reached from the fact that 1, 2-dichlorethane exists in only one modification?

4. Outline clearly the experimental evidence for the structural formulas of the following compounds: allyl alcohol, maleic anhydride, ketene, acrolein.

5. Outline reactions for the preparation of the following: (a) allyl iodide from glycerol; (b) crotonaldehyde; (c) acrylic acid from trimethylene glycol; (d) butanol-2 from glycerol; (e) ethyl acetate from acetone.

6. Define the following terms: free rotation, vinyl alcohol, 1, 4 addition, three-atom system, antioxidants, partial valences.

7. Write equations showing four general methods of preparing  $\alpha, \beta$ -unsaturated acids. Outline a procedure for preparing  $\text{C}_2\text{H}_5\text{CH} = \text{CHCOOH}$  from ethyl alcohol by two different methods.

8. Why can not acrylic acid be prepared by oxidizing allyl alcohol with potassium permanganate or chromic acid? How would you prepare acrylic acid from glycerol?

9. Write structural formulas for the following substances: penten-2-oic acid; 3-methylheptadiene-2, 5-oic acid; 2-methylbuten-3-ol-2; vinyl propionate; dimethyl ketene; phorone; mesityl oxide.

10. Write reactions for the preparation of the following: (a)  $(\text{CH}_3)_2\text{C} = \text{CHCHOHCH}_3$ ; (b)  $\text{CH}_3\text{CH}_2 - \text{CH}_2\text{CH} = \text{CH}_2$ ; (c)  $\text{CH}_3\text{CH} = \text{CHCH}_2\text{COOH}$ .

11. Compare the structural formula of carbon suboxide with that of a ketene. What reaction would you expect between the oxide and (a) water, (b) alcohol, (c) ammonia?

## CHAPTER XVII

### THE CARBOHYDRATES

Sugar, starch and cellulose are common examples of a class of substances known as the carbohydrates. This name originated from the fact that the empirical formula of these compounds and many other carbohydrates can be written as  $C_x(H_2O)_x$ ; for example, glucose,  $C_6H_{12}O_6$ ,  $(C_6(H_2O)_6)$  and cane sugar,  $C_{12}H_{22}O_{11}$ ,  $(C_{12}(H_2O)_{11})$ . Such formulas have no structural significance, of course.

The carbohydrates are divided into three classes: the **monosaccharides**, the **disaccharides**, and the **polysaccharides**. The monosaccharides are **polyhydroxy aldehydes** or **polyhydroxy ketones**. The disaccharides and polysaccharides, on hydrolysis, yield monosaccharides. A knowledge of the monosaccharides, therefore, is essential to an understanding of the more complex carbohydrates.

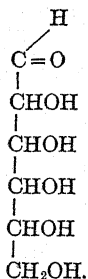
#### MONOSACCHARIDES

**Glucose**,  $C_6H_{12}O_6$ , also known as dextrose or grape sugar, is the commonest monosaccharide and occurs widely distributed in nature. Its commercial manufacture from starch will be discussed later (p. 316). In considering the structural formula for glucose, it is simplest first to look back fifty years and disregard modern developments in sugar chemistry. The simple open chain formula, which was at that time satisfactory, will be discussed in the following paragraphs although we now know that it is incorrect. The old formula is still useful in indicating many of the reactions of glucose, and we shall use it for this purpose throughout this book.

**Structure of Glucose.** The following facts are of importance in determining the constitution of glucose: (1) glucose is easily oxidized to an acid of the formula  $C_6H_{12}O_7$ ; (2) it forms a pentaacetate,  $C_6H_7O(OCOCH_3)_5$ , when treated with acetic anhydride; (3) on reduction with hydrogen iodide and phosphorus (above  $100^\circ$ ), a mixture of *n*-hexyl iodide and secondary hexyl iodide is formed. From this third fact we can conclude that the six carbon atoms in glucose are arranged in a straight chain, and from the second, that there are five hydroxyl groups in the molecule.

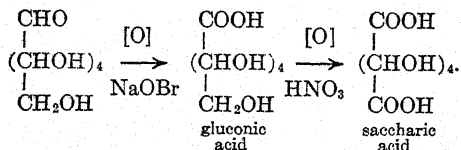
The oxidation reaction indicates that the substance is an aldehyde. In connection with this last conclusion it will be recalled that an aldehyde  $RCHO$  is easily oxidized to an acid  $RCOOH$ ; primary alcohols are also oxidized to acids, but there is a loss of two hydrogen atoms. The acid from glucose has the same number of both carbon and hydrogen atoms as the sugar itself and, therefore, an aldehyde group and not an alcohol group is involved in the oxidation. One of the five hydroxyl groups is that of a primary alcohol since a *dibasic* acid with six carbon atoms (and four OH groups) can be prepared by drastic oxidation.

Since it has been found that the occurrence of two or more hydroxyl groups on the *same* carbon atom is very unusual, we may distribute the 5 OH groups on five of the six carbon atoms of the straight chain. This leaves the terminal carbon atom for the aldehydic group as follows:

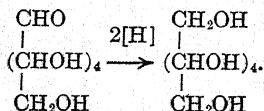


This is the old formula for glucose; the newer cyclic formula which explains the existence of certain derivatives and isomeric forms will be referred to later (p. 307).

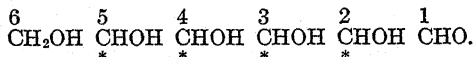
The *oxidation of glucose* to a monobasic acid, **gluconic acid**, and to a dibasic acid, **saccharic acid**, may be represented as follows:



The *reduction of glucose* proceeds readily with sodium amalgam yielding a hexahydroxy compound, **sorbitol** or **sorbite** (p. 191):



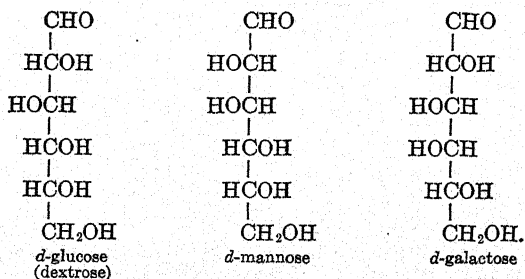
**The Aldohexoses.** The formula for glucose shows the existence of four asymmetric carbon atoms (indicated by stars):



The number of possible stereoisomers of a substance with this formula is  $2^4$  or 16. Glucose is only one of these 16 isomers; it is scientifically known as *d*-glucose, its enantiomorph as *l*-glucose. All the isomers are known; some occur in nature and others have been prepared in the laboratory. This group of sixteen stereoisomers is known as the *group of aldohexoses*.

Sugars which have an aldehydic group are called **aldoses**; those which contain a ketonic group **ketoses**. The number of carbon atoms in the sugar can also be indicated in the name. Thus, the **hexoses** are all sugars with six carbon atoms; the **pentoses** with five. The name aldohexose indicates a six carbon sugar with an aldehydic group. Similarly the name aldopentose indicates a five carbon sugar with an aldehydic group and the name ketohexose a ketonic sugar with six carbon atoms.

The methods of determining the spatial relationship of the asymmetric atoms in the isomeric sugars are so complicated that the subject is often reserved for a later course. In the last chapter of this book, some illustrations of the methods employed are outlined for those who may be interested. The results of such stereochemical investigations are represented by three-dimensional models which may be projected on a plane by the same conventions as used in the case of tartaric acid (p. 226). When this is done the *configuration* (*i.e.*, spatial relationship of the atoms) of some of the commoner aldohexoses is as follows:

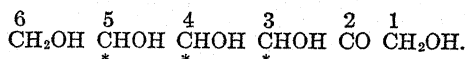


The prefixes *d* and *l* in the names of the carbohydrates and related substances do not refer to the sign of their optical activity,

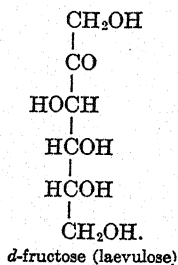
but to the spatial relation of the groups (*i.e.*, the configuration). To those who are versed in the stereochemistry of the sugars, these letters signify the relationships of the three-dimensional formulas. The formulas for *l*-glucose, *l*-mannose, and *l*-galactose would be the mirror images of those shown above, of course. (For a further consideration see Chap. XXXIII.)

**Other Aldohexoses of Importance.** Besides the very important sugar, *d*-glucose (dextrose), two other of the sixteen possible isomers should be particularly mentioned. These are *d*-mannose and *d*-galactose whose configurations have just been represented. It will be noted that mannose differs from glucose only by having the opposite spatial arrangement of the hydroxyl group nearest the carbonyl. It is, therefore, said to be the *epimer* of glucose. It may be prepared by the hydrolysis of ivory nut fragments. *d*-Galactose is contained in the cell walls of plants in polymerized anhydro forms known as galactans. It is formed by the hydrolysis of such substances and of other vegetable materials known as pectins. Together with *d*-glucose, it is formed by the hydrolysis of milk sugar (lactose).

**Laevulose, a Ketohexose.** The ketohexoses are a class of sugars represented by the following general formula (asymmetric atoms indicated by stars):



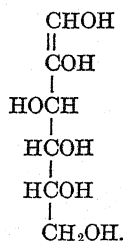
There are  $2^3$  or 8 isomeric ketohexoses. Of these only one is of general interest. This is *d*-fructose, commonly called laevulose or fruit sugar. The configurational formula is as follows:



The nomenclature of this sugar illustrates the fact that the prefix does not refer to the sign of rotation. The sugar is actually laevorotatory as the name laevulose implies. It is called *d*-fructose rather than *l*-fructose because it is closely related to *d*-glucose.

Indeed, the close relationship is evident by comparing the configurational formulas. Such a comparison reveals that *d*-glucose, *d*-mannose, and *d*-fruc-

tose are identical in respect to the configurations of the three asymmetric carbon atoms nearest the  $\text{CH}_2\text{OH}$  group (bottom of formula as usually written). It is therefore not surprising that each of these sugars on treatment with dilute alkali passes into an equilibrium mixture which contains some of each of all three. This conversion probably proceeds through an enolic form (ene-diol) common to all three. Its formula would be:



ene-diol of glucose, mannose, fructose

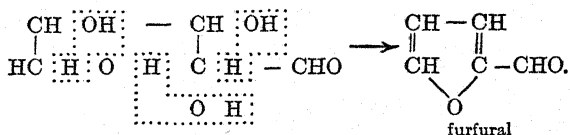
**Structure of *d*-Fructose.** The structural formula of *d*-fructose as a ketohexose is established by the following facts. It forms a penta-acetate, and therefore the molecule contains five hydroxyl groups. On reduction it yields a hexahydroxy compound (*d*-sorbitol) with two more hydrogen atoms in the molecule than the original sugar. It is therefore *either* an aldehyde or a ketone. Even on cautious oxidation two carbon atoms are lost, and a monobasic acid is formed. This proves that the compound is a ketone and not an aldehyde, and that the ketonic group is the second group in the chain. (The other oxidation product is glycollic acid,  $\text{CH}_2\text{OHCOOH}$ .) The reduction of *d*-fructose to the same hexahydroxy compound as was obtained from glucose proves that the same chain is present in both compounds.

*d*-Fructose occurs in many fruits and, together with dextrose, is a product of the hydrolysis of cane sugar. It is best prepared by the hydrolysis of a polysaccharide, *inulin*, which occurs in dahlia tubers and the Jerusalem artichoke.

**The Aldopentoses.** Of the eight isomeric aldopentoses only three are of general interest. Two are formed by the hydrolysis of polysaccharides of high molecular weight known as **pentosans**. These are *l*-arabinose and *d*-xylose (both compounds are dextrorotatory though *l*-arabinose is related to *l*-glucose). The pentosans together with similar compounds which yield mannose or galactose on hydrolysis are known as *hemi-celluloses*. They occur widely distributed in plants particularly associated with cellulose in cell walls. Cherry gum consists largely of a pentosan which yields

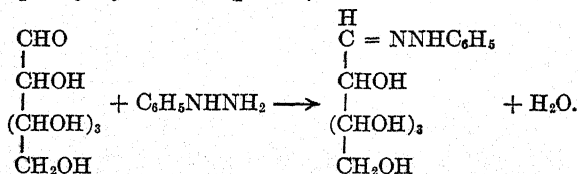
*l*-arabinose on hydrolysis. *d*-Xylose is obtained by the hydrolysis of straw or bran. The third pentose of importance is *d*-ribose which occurs in nucleic acids and a number of other compounds of interest to the biochemist.

The aldopentoses resemble the aldohexoses closely in most of their reactions. The action of hot hydrochloric or sulfuric acid serves to differentiate the two classes; only the pentoses form a volatile aldehyde known as **furfural**. This substance contains a five membered ring containing oxygen. Its presence can be detected by the characteristic colored products it forms on condensing with certain compounds.



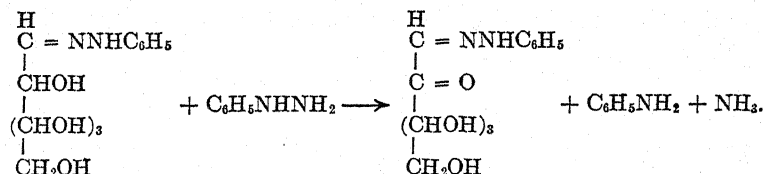
#### REACTIONS OF THE MONOSACCHARIDES

Both the ketoses and aldoses are oxidized by warm Fehling's solution and warm ammoniacal silver nitrate. This is somewhat surprising in the case of the ketose, since ketones are not usually attacked by these reagents. The ketoses differ from the aldoses in that the latter, on cautious oxidation with bromine water, yield an acid with the same number of carbon atoms; this is not possible in the case of the ketoses which yield acids with fewer atoms. Neither aldoses nor ketoses give the characteristic aldehyde test with Schiff's reagent (p. 124). Both react with phenylhydrazine (p. 122),  $\text{C}_6\text{H}_5\text{NHNH}_2$ , to form yellow crystalline **osazones** which are less soluble than the sugars. This reaction was discovered by Emil Fischer<sup>1</sup> and is of great value in identifying and purifying the monosaccharides. The first step in the reaction is the formation of a phenylhydrazone (p. 122):

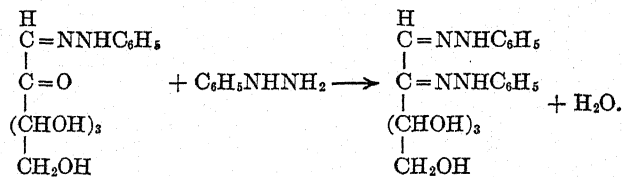


<sup>1</sup> Emil Fischer (1852-1919). Professor at the University of Berlin; the successor to A. W. von Hofmann (p. 151). His discovery of phenylhydrazine was made in 1875 at Strassburg; it was not until some years later that he applied this reagent to a study of the sugar series. It is largely due to his labors that the relationship of the isomeric pentoses and hexoses was finally established.

The reaction proceeds further; the hydroxyl group next to the terminal group is oxidized by one molecule of phenylhydrazine, which is reduced to a substance known as aniline ( $\text{C}_6\text{H}_5\text{NH}_2$ ) and ammonia:



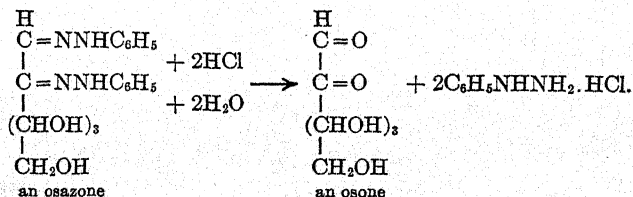
The ketone group generated by this oxidation then condenses with another molecule of phenylhydrazine, forming the osazone, which is thus a sort of double phenylhydrazone:



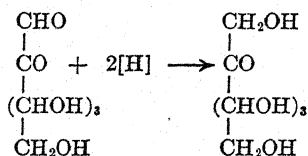
A similar reaction takes place with ketoses, except that here the terminal  $\text{CH}_2\text{OH}$  group next to the  $\text{CO}$  group is involved in the oxidation. It is possible to isolate the phenylhydrazones before the reaction proceeds further.

Sugars which are identical except for the first two carbon atoms (atoms 1 and 2) will yield the same osazone. Thus, *d*-glucose, *d*-mannose, and *d*-fructose when treated with an excess of phenylhydrazine all form the same osazone. This fact is very useful in relating these three substances, since it proves that the configuration of the three asymmetric atoms nearest the  $\text{CH}_2\text{OH}$  group (atoms 3, 4, and 5) is the same in all three compounds.

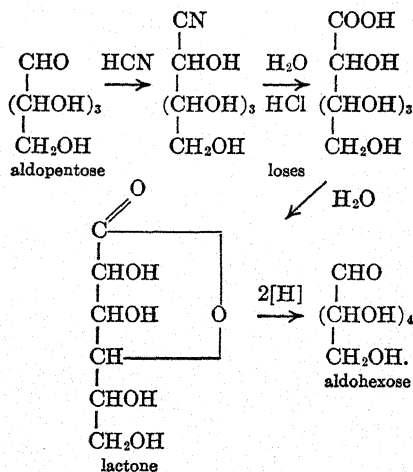
**Conversion of an Aldose to Ketose.** When an osazone is warmed with concentrated hydrochloric acid, hydrolysis takes place and a keto-aldehyde known as an **osone** is formed:



The osones are readily reduced to ketoses.

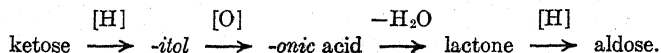


**Lengthening the Carbon Chain.** The carbon chain of an aldose may be lengthened by a series of reactions. This process is very useful as it enables one to prepare hexoses from pentoses, and thus relate the two classes of compounds. The fundamental reactions are two — the first the preparation of an  $\alpha$ -hydroxy acid from an aldehyde by a process we have met before (p. 211); the second is the reduction of this hydroxy acid to the corresponding aldehyde. This takes place in this case because the hydroxy acid spontaneously forms a lactone which is really reduced to the aldehyde. The following equations will illustrate the procedure in the case of preparing an aldohexose from an aldopentose:

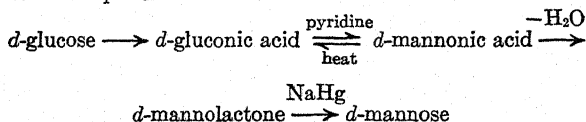


This same set of reactions may be used in converting a *ketose to an aldose*. The ketose is first reduced to the hexahydroxy compound. This is then cautiously oxidized to the acid. This acid (in the form of its lactone) is then reduced to the aldose. The difficulty in this process is that when the hexahydroxy compound is formed it has two points of attack for the oxidizing agent; the oxidation has to be carefully controlled as otherwise a dibasic acid is formed. The names of the polyhydric compounds formed by reducing the

sugars always end in *-itol* (see p. 191); the corresponding monobasic acids have a name ending in *-onic*. We may therefore summarize the process thus:



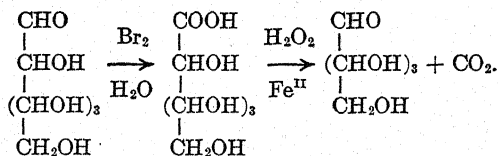
**Epimerization.** On heating an aqueous solution of an *-onic* acid with pyridine, part of the acid undergoes epimerization; that is, the carbon atom adjacent to the carboxyl group assumes the opposite configuration. This is a reversible reaction which comes to equilibrium. The mixture of the two acids present in this reaction can generally be separated without difficulty through their salts. Since the *-onic* acids, as lactones, can be reduced by sodium amalgam, epimerization is a useful reaction for preparing one sugar from another. The conversion of *d*-glucose to *d*-mannose illustrates the conversion of an aldose to its epimer:



It seems probable that epimerization of the *-onic* acids proceeds because the hydrogen on the alpha carbon can enolize and the enolic form, in which the asymmetry of the  $\alpha$  carbon atom has disappeared, may revert either to the original acid or its epimer. This may be illustrated thus:

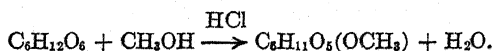


**Degradation of Carbon Chain.** There are several methods of degrading an aldose to the sugar with one less carbon atom. The simplest method is to oxidize the aldose with bromine water to the corresponding acid (the *-onic* acid). This is an  $\alpha$ -hydroxy acid and can therefore be oxidized to the corresponding aldehyde (p. 214) with loss of carbon dioxide. The reagent used in the sugar series is hydrogen peroxide and a trace of ferrous salt.



**Glucosides.** Glucosides are derivatives of glucose which on boiling with dilute acid are easily hydrolyzed, forming glucose and an hydroxy compound. Many glucosides occur in nature, an extraordinary variety of hydroxy compounds being thus combined. Methyl glucoside is readily formed by the interaction of glucose and methyl alcohol in the presence of hydrochloric acid.

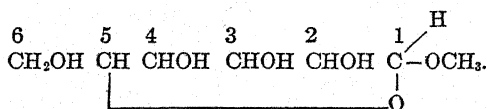
The reaction involves the elimination of one molecule of water,



The glucosides differ markedly from glucose in their reactions. Thus, they do not reduce Fehling's solution. This fact, their mode of formation and their easy hydrolysis show that they are

closely related to the acetals,  $\text{RC} \begin{array}{c} \text{H} \\ \diagup \\ \text{OR}' \\ \diagdown \\ \text{OR}' \end{array}$  (p. 121). The following

formula for methyl glucoside shows that it may be considered as an acetal in which one of the OR' groups is derived from methyl alcohol, the other from an OH group in the molecule itself,

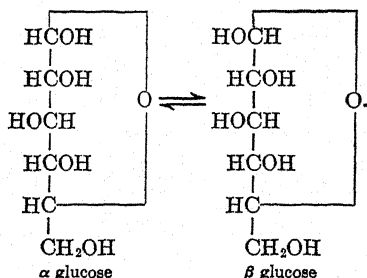


All aldoses and ketoses, when treated with an alcohol in the presence of a catalyst, form compounds similar to the glucosides; these are given the general name **glycosides**. In most cases two isomeric forms can be obtained known as the **alpha** and **beta**. These differ in their physical properties, particularly in their rotatory power. These isomers are predicted from the theory of stereoisomerism. There are *five* asymmetric carbon atoms in methyl glucoside (atoms 1-5). The interaction with the alcohol makes the terminal atom asymmetric; corresponding to this asymmetric atom, there are two stereoisomers. In one, the terminal atom is *laevo*-rotatory; in the other, it is *dextro*-rotatory. Although a vast number of the naturally occurring glycosides are glucose derivatives, glycosides of other hexoses and of pentoses are found in plant and animal products.

**The Cyclic Structure of Glucose.** We have just seen that the existence of two isomeric methyl glucosides is a necessary consequence of the cyclic structure. This fact provides the clue to the explanation of two isomeric forms of glucose itself. These are known as **alpha glucose** and **beta glucose**. The former crystallizes from water as a hydrate, the latter is anhydrous. A freshly prepared aqueous solution of the alpha form has a specific rotation of  $+109.6^\circ$ ; a similar solution of the beta form has a specific rota-

tion of  $+20.5^\circ$ . On standing, the specific rotation of both solutions slowly changes until a final value of  $+52.3^\circ$  is reached in both cases. This corresponds to an equilibrium mixture of the two forms. This change is known as **mutorotation**.

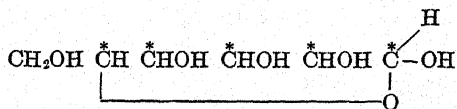
The two isomeric forms of glucose are clearly parallel to the two isomeric methyl glucosides discussed above. Alpha and beta glucose correspond respectively to a laevo and a dextro rotation of the *terminal* atom. Their existence shows that the old open chain aldehydic formula is incorrect, and in its place we must write the following cyclic structures:



The ease with which the two isomers pass into each other is in marked contrast to the stability of the two isomeric methyl glucosides. In the case of glucose the migration of a hydrogen atom can take place as in keto-enol tautomerism. It is probable that both forms are in equilibrium with a very small amount of an open chain aldehydic form corresponding to the old formula for glucose,

$\alpha$  glucose (cyclic)  $\rightleftharpoons$  open chain aldehyde  $\rightleftharpoons$   $\beta$  glucose (cyclic).

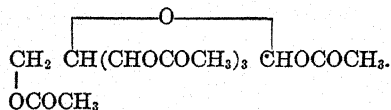
If we consider the cyclic formula as a general formula for the aldohexoses, it is evident that  $2^5$  or 32 isomers are predicted,



in place of the  $2^4$  or 16 on the basis of the open chain formula. A careful study of each of the aldohexoses has shown the existence of two forms corresponding to alpha and beta glucose. Thus, the number of isomeric aldohexoses now known is greater than can be accounted for on the open chain formula; in time we may expect

that all the 32 isomers corresponding to the cyclic formula will be prepared.

The reactions of the aldohexose we have previously written as though they involved an open chain aldehyde form. This may still be correct, as a small amount of the free aldehydic form may be in equilibrium in solution. If this reacts in the usual way with the reagent, it is used up and more of the cyclic forms open; eventually the entire reaction proceeds to completion. It is also possible that the cyclic forms themselves react directly, and that the oxygen ring opens under the influence of the reagent but not before. On this basis one can write suitable equations for all the reactions of aldohexoses. **Glucose penta-acetate** which is formed from glucose and acetic anhydride has none of the typical reactions of glucose itself and exists in an alpha and beta form. It, therefore, has the following cyclic structure:

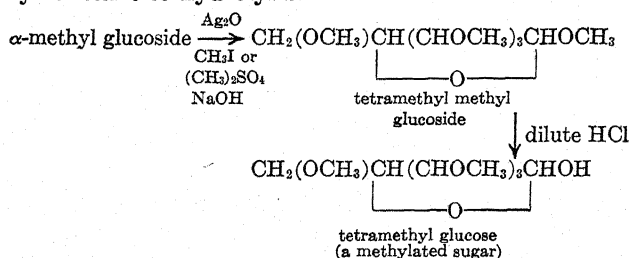


**The Size of the Ring.** Even after it became clear that the explanation of the two forms of glucose was to be found in the fact that this substance had a cyclic structure, the size of the ring was uncertain. In the formulas on the preceding page, a six-membered ring is shown. It is evident that formulas can also be written for analogous cyclic compounds in which smaller or larger rings exist. The determination of the exact ring structure of each sugar derivative marked the final stage in the development of the structural chemistry of this class of compounds.

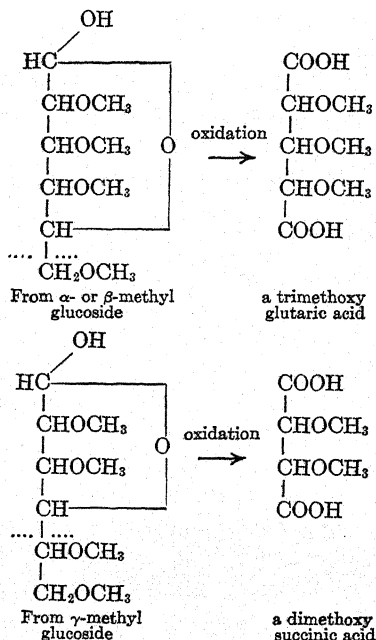
Briefly, the method of determining the ring structure consists in replacing all the hydrogen atoms of the hydroxyl groups by methyl groups and then transforming the resulting methylated sugar to compounds in which the position of the methoxyl groups ( $-\text{OCH}_3$ ) could be located. It should be noted that as long as one is dealing with the sugar itself the reversible opening and closing of oxide rings of several sizes is possible. When all hydroxyl groups, except the potential aldehydic group, have been converted into methoxy groups, however, the size of the ring is fixed. From that point on the usual methods of organic chemistry will yield information as to the structure.

The methylation of sugars is carried out by first converting the

sugar to the methyl glycoside, treating this compound with silver oxide and methyl iodide or dimethyl sulfate in alkaline solution. The glycoside methyl group is then removed by hydrolysis with acid. The other methoxy groups being ethers, it should be noted, are very resistant to hydrolysis.

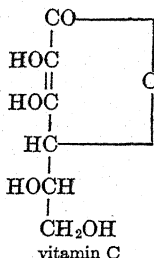


**Furanose and Pyranose Sugars.** The oxidation of the tetramethyl glucose prepared from either  $\alpha$ - or  $\beta$ -methyl glucoside yields a trimethoxy glutaric acid. This proves the presence of a six-membered ring in these glucosides. Another methyl glucoside ( $\gamma$ -methyl glucoside) can also be prepared from glucose. It has been shown to contain a *five*-membered ring, since the tetramethyl glucose obtained from this third glucoside by the procedure outlined above did not yield a *trimethoxy* but a *dimethoxy* acid (dimethoxysuccinic acid) on oxidation.



Sugars and sugar derivatives which contain six-membered rings are said to be in the *pyranose* form; those which contain a five-membered ring are called *furanose* compounds. The glycosides which are obtained by the usual procedure from the aldohexose and aldopentose all contain the pyranose structure. The furanose ring, however, is present in a number of aldoketose derivatives which occur in nature, including cane sugar (see below).

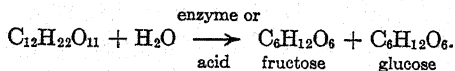
**Ascorbic Acid, Vitamin C.** Ascorbic acid is present in a great variety of vegetables and in particular in citrus fruits. It is a strong reducing agent, reducing both ammoniacal silver nitrate and Fehling's solution in the cold. This behavior is due to the presence of an **ene-diol** system in the molecule:



Ascorbic acid is a sufficiently strong acid to react with sodium carbonate solutions; the acidity is due to one of the hydrogens of the ene-diol system. Since it is also a lactone, it may be opened by treatment with alkali. The absence of ascorbic acid from an otherwise normal diet ultimately leads to scurvy. This vitamin is now manufactured synthetically by a series of reactions which start with *d*-glucose.

#### DISACCHARIDES

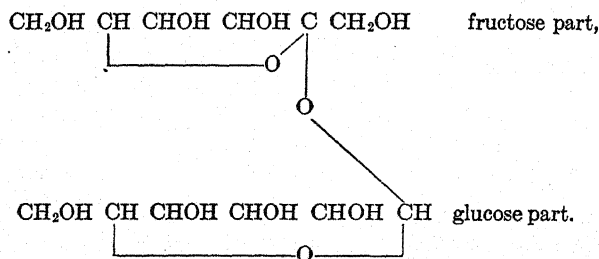
**Sucrose** or cane sugar,  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ , is the most familiar sugar. It is readily hydrolyzed in the presence of a little acid or by the action of the enzyme *invertase*; the products of hydrolysis are one molecule of glucose and one of fructose:



This reaction is called **inversion** because the mixture of products rotates the plane of polarized light in the opposite direction from pure sucrose, which is dextrorotatory. Since fructose is laevorotatory and glucose dextrorotatory, one might imagine that an

equimolar mixture of the two would be inactive. This is not the case, however, because the action of fructose is more powerful than that of glucose; a mixture of the two in equal amounts therefore rotates the plane of polarized light to the left. The name **invert sugar** is applied to a mixture of glucose and fructose.

The hydrolysis of sucrose establishes the fact that its molecule is built up of one of glucose and one of fructose joined together with the loss of water. The ease with which the hydrolysis takes place suggests that the nature of the linkage is similar to that in the glucosides. Sucrose does not reduce Fehling's solution. This fact indicates that neither the aldehydic nor ketonic groups of the constituent monosaccharides are free in the disaccharide. The following formula represents the sucrose molecule:



It will be noted that the fructose part of the molecule contains a five-membered ring (furanose form of fructose), the glucose a six-membered ring. This was established by methylation of the disaccharide followed by hydrolysis and determining of the structure of the two methylated hexoses.

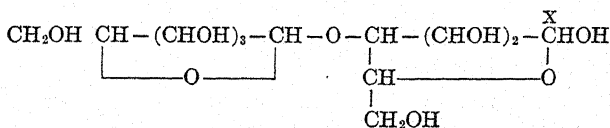
**Maltose and Lactose.** Two other disaccharides are of general interest; they are maltose and lactose. They both crystallize with a molecule of water of crystallization and have the molecular formula  $\text{C}_{12}\text{H}_{22}\text{O}_{11} \cdot \text{H}_2\text{O}$ . **Maltose** is the product of the enzymatic hydrolysis of starch. This hydrolysis is the first step in the digestion of starchy foods; the saliva contains an enzyme, **ptyalin**, which rapidly converts starch into maltose. Maltose is the sugar produced by the action of diastase (from malt) on starch, and its biochemical transformation to alcohol was mentioned in the first chapter of this book (p. 16). On hydrolysis maltose yields two molecules of glucose. This hydrolysis to glucose is the first step in the formation of alcohol from maltose. The reaction is brought about by an enzyme present in the yeast. The glucose thus pro-

duced is then fermented to alcohol by another enzyme in the yeast cell (zymase).

**Lactose** is the sugar which occurs in milk. It is present to the extent of about 4 per cent. On hydrolysis it yields a molecule of glucose and one of **galactose**. Lactose is fermented to lactic acid by the lactic acid ferment which is responsible for the souring of milk (p. 212); it is not fermented by ordinary yeast.

Both *maltose* and *lactose* are **reducing sugars** like the monosaccharides. That is, they are oxidized by warm Fehling's solution. In this respect they differ from sucrose which has no action on Fehling's solution. The reason for this difference is seen by comparing the formula for sucrose with that for maltose or lactose which is given below. Maltose and lactose both have one of the original aldehydic groups of glucose still free in the molecule (shown by a cross in the cyclic form written below). The free terminal group in maltose or lactose (a potential aldehyde group) confers on these disaccharides all the properties of aldoses. Glucose, on the other hand, has no such group. It is both a glucoside and a fructoside in which the monosaccharide residues are joined together through the potential aldehydic group of glucose and the potential keto group of fructose.

In both disaccharides, only pyranose rings are involved. This was established by methylation and degradation of the methylated sugars.



maltose or lactose

(In maltose the sugar residue on the right is glucose;  
in lactose it is the isomeric galactose.)

**Enzymatic Hydrolysis of Glucosides.** The disaccharides may be regarded as glucosides. This is evident from the formula for maltose written above; one molecule of glucose (written on the right) is in place of the methyl alcohol which has condensed with glucose in the methyl glucosides. It will be recalled that there are two isomeric glucosides possible in each case which we designate as *alpha* or *beta*. It has been found that there are enzymes which *specifically* hydrolyze the one form of glucoside or the other. These enzymes act almost independently of the nature of the

hydroxy compound condensed with the glucose residue. One of these enzymes is known as **maltase**, because it hydrolyzes this sugar to two molecules of glucose. It occurs widely distributed in nature; for example, in yeast and in the pancreas. It acts on all the glucosides of the one series which are known as the *alpha glucosides*. The other enzyme is known as **emulsin** and hydrolyzes only *beta glucosides*. Both enzymes are very specific and will not act on the glucoside of the other configuration. Once this fact had been established, it was possible to use these enzymes in determining the configuration of a glucoside.

### POLYSACCHARIDES

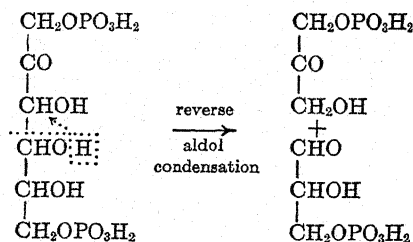
**Starch, glycogen** (animal starch), and **cellulose** are all substances of large molecular weight which on hydrolysis yield glucose. They may all be represented by the empirical formula  $(C_6H_{10}O_5)_x$  or  $(C_{12}H_{20}O_{10})_n$ . The polysaccharides are either insoluble in water and organic solvents, or only slightly soluble, forming colloidal solutions. They do not show the aldehydic reactions of monosaccharides; the presence of three hydroxyl groups connected with each group of six carbon atoms is readily demonstrated by acetylation with acetic anhydride.

While the molecules of the three important polysaccharides mentioned above are composed of only glucose molecules joined together, the class includes other types of compounds. For example, **inulin** is a polysaccharide which on hydrolysis yields the ketohexose, fructose.

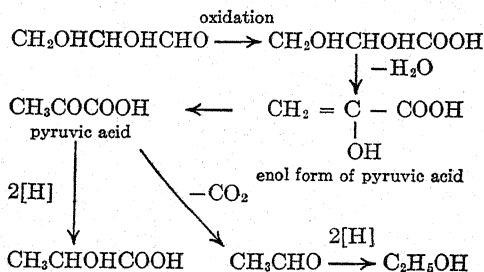
### *Starch and Glycogen*

**Occurrence in Food-Stuffs.** Starch occurs as white granules in nearly all plants. Starch granules from different plants differ greatly in size and shape. The food value of cereals and many other vegetable foods is due primarily to the starch which is present in them. For example, *rice* is about 75 per cent starch, *corn* 50 per cent and *potatoes* 20 per cent. This starch is hydrolyzed to maltose and then glucose in the process of digestion in the animal body. The liver then converts the glucose to a polysaccharide known as **glycogen**. This substance is very similar to starch. Indirectly, its combustion furnishes the heat and energy necessary for the life of the higher animals.

**Biological Conversion of Hexoses to Trioses.** In the conversion of glycogen to lactic acid (p. 212) in the muscle of animals and in the fermentation of glucose to alcohol by yeast, the fundamental reaction is the cleavage of a hexose molecule into two molecules of a three-carbon sugar. The three-carbon sugars are called trioses. The ketose of this group is dihydroxy acetone  $\text{CH}_2\text{OHCOCH}_2\text{OH}$ ; the aldose is glyceric aldehyde  $\text{CH}_2\text{OHCHOHCHO}$ . The close relation of these two substances to a hexose will be evident when one considers that an aldol condensation of the two would produce fructose. By a reverse aldol reaction (p. 118) fructose would yield these two substances. Actually in nature the process is brought about by enzymes and as a first step the hexose is converted into a mono- or a diphosphate (probably a fructose diphosphate). The transformation of this compound into the monophosphoric acid ester of dihydroxy acetone and glyceric aldehyde has been shown to be one of the essential steps in the chain of reactions, starting with glycogen, by which muscle tissue receives its energy.



Since the two trioses have the same di-enol form they are interconvertible. Glyceric aldehyde on oxidation and loss of water yields pyruvic acid; loss of carbon dioxide from this acid yields acetaldehyde. The reduction of pyruvic acid yields lactic acid. If acetaldehyde is itself reduced, ethyl alcohol results:



In the cell the changes involve not the hydroxyl compounds shown above but their phosphoric acid esters. These are formed by enzymatic action which involves a substance known as **adenylic acid pyrophosphate** (p. 527), containing two phosphoric acid radicals, one of which can be transferred to the carbohydrate. If the oxidation of glyceric aldehyde and the reduction of pyruvic acid are so interrelated that one reaction proceeds at the expense of the other,

it is clear the over-all result is the change of a hexose molecule to two molecules of lactic acid. This is a very much simplified statement of the chemical change which occurs in contracting muscle in the absence of oxygen. If carbon dioxide has been lost from pyruvic acid and the oxidation of glyceric aldehyde takes place at the expense of the reduction of acetaldehyde, the over-all change has been the conversion of one molecule of hexose into two molecules of alcohol and two of carbon dioxide. This is an equally over-simplified account of fermentation. If the pyruvic acid (or its precursor, the triose) is oxidized by atmospheric oxygen (by means of a series of oxidation enzymes) and the process continues to completion, the over-all reaction is the complete combustion of the hexose to carbon dioxide and water.

**Structure of Starch and Glycogen.** It has been established that the molecule of both starch and glycogen is composed of a chain of maltose units. In the case of starch 13 to 15 such units are joined together while in glycogen the number appears to be less (6 to 9). On enzymatic hydrolysis the glycosidic link between the units is broken and starch can be converted into maltose. Further hydrolysis yields, of course, glucose.

**Chemical Behavior of Starch.** Starch is practically insoluble in cold water, but when a suspension of starch in water is heated, the granules swell and form a viscous solution which on cooling sets to a jelly. On dilution a colloidal solution of starch can be obtained which is liquid at room temperature. Such a solution shows none of the characteristic reactions of a monosaccharide. If it is boiled with dilute hydrochloric acid, the starch is completely hydrolyzed to glucose. If the enzyme diastase is allowed to act on a suspension or solution of starch, a solution of maltose results. Starch gives a characteristic blue color with iodine; the test is very delicate. Dextrine yields a color with iodine which varies from red to violet, whereas no color is formed when the mono- and disaccharides are treated in the same manner.

**Manufacture of Starch, Glucose, and Dextrine.** Starch is usually prepared commercially from corn or potatoes by a mechanical process of grinding and washing. A suspension of impure starch in water is thus obtained; by allowing it to settle slowly, the impurities are deposited first and may be removed. A microscopic examination of starch will reveal the source of the material, as the granules are characteristic of the plant from which they come. Starch is used in laundry work, in cooking, in the manufacture of pastes, and in the preparation of dextrines and glucose (see below).

The hydrolysis of starch to glucose is carried out on a very large manufacturing scale. A few per cent of hydrochloric acid is used as the catalyst, and after the completion of the hydrolysis this is carefully neutralized. The evaporation of the glucose solution thus prepared yields thick, syrupy solutions,

which are widely sold as sweetening materials for domestic use and in the manufacture of candy.

When dry starch is heated to 200°–250°, a material known as **dextrine** is produced. It is soluble in cold water yielding a syrupy solution which has strong adhesive properties. Dextrine is used in manufacturing the mucilage used on postage stamps. From its behavior, dextrine appears to be a polysaccharide of smaller molecular weight than starch. On hydrolysis it yields glucose. Dextrines are also formed as intermediate compounds in the enzymatic hydrolysis of starch to maltose.

### *Cellulose*

**Common Forms of Cellulose.** The structural material of the plant world is largely cellulose. It is the substance present in vegetable fibers and fabrics. Pure filter paper and "cotton wool" are examples of nearly pure cellulose. As in the case of starch, a microscopic examination will reveal differences in the cellulose fibers obtained from different sources.

In wood the cellulose fibers are embedded in an amorphous material of high molecular weight known as **lignin**. In the manufacture of cellulose from wood, the operations are designed to remove this lignin and hemi-cellulose (p. 302). The cellulose fibers can be separated from these materials by treatment with such reagents as sodium hydroxide or calcium bisulfite which decompose or dissolve the lignin.

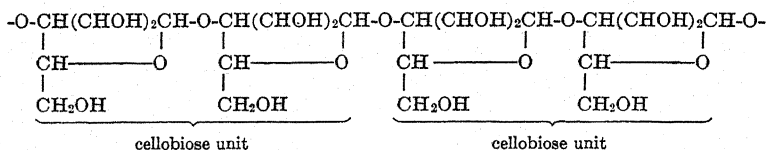
The manufacture of paper from wood consists essentially in separating the cellulose and then matting the fibers together. The cheaper papers are prepared from mechanical pulp which is merely soft wood disintegrated in a stream of water. Lignin and other impurities are present, and their presence can be shown by a yellow coloration with aniline hydrochloride solution.

**Properties.** Cellulose is insoluble in water and all organic solvents. It dissolves in Schweitzer's reagent (an ammoniacal solution of copper hydroxide) probably because of a chemical reaction. On acidification the cellulose is precipitated.

Cellulose is much more resistant to hydrolysis than starch and is attacked only slowly by boiling with dilute acids. Cellulose dissolves in concentrated sulfuric acid; on diluting the solution and boiling it, glucose is formed as the final product.

**Chemical Constitution of Cellulose.** On careful hydrolysis of cellulose, a disaccharide, cellobiose, is formed. This disaccharide on further hydrolysis yields two molecules of glucose. It has been shown that cellobiose has the same structural formula as

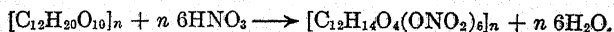
maltose (p. 313) except that it is a beta glucoside while maltose is an alpha glucoside. Small amounts of tri- and tetra-saccharides have also been isolated from the hydrolysis of cellulose. The cellulose molecule is composed of a long chain of cellobiose molecules joined together as illustrated below. It appears to contain 50 to 100 cellobiose units. About fifty such chains are arranged in a bundle which is called a *micelle*. A cellulose micelle is about 50A thick and 500 to 1000A long. A cellulose fiber is in turn made up of a large number of these micelle groups.



It will be evident that starch and cellulose differ both in the length of the chain and in the stereochemical nature of the glycosidic link. Starch is related to the alpha glucoside, cellulose to the beta.

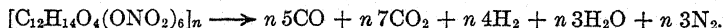
**Glucose from Wood.** Since wood is an excellent and a cheap source of cellulose, its transformation to simple sugars is carried out today in Germany by the **Bergius process**. In this method wood is treated with concentrated hydrochloric acid during which the cellulose is hydrolyzed and the insoluble lignin precipitated. The products obtained consist chiefly of glucose along with other simple sugars. It is claimed that as much as 66 per cent of the weight of wood is converted into sugars. Acetic acid is also a by-product of this process.

**Cellulose Nitrates.** The hydroxyl groups in the polysaccharides form esters as would be expected. The esters of nitric acid can be formed by the direct action of a mixture of nitric and sulfuric acids on the polysaccharide. The cellulose nitrates which are prepared in this way are substances of very great importance. They are often erroneously called nitrocellulose. If the reaction is carried out in such a manner that all the free hydroxyl groups are esterified, the material is known as highly nitrated cotton or **gun cotton**. It is used as a high explosive in torpedoes. It has the empirical formula  $[\text{C}_6\text{H}_7\text{O}_2(\text{ONO}_2)_3]_n$  or  $[\text{C}_{12}\text{H}_{14}\text{O}_4(\text{ONO}_2)_6]_n$ . It should be noted that since the molecular weight of cellulose is unknown we may express the analysis either in terms of a unit of 6 or 12 carbon atoms.



The lower nitrates of cotton are called **pyroxylin**. They are important because they are soluble in mixtures of various organic solvents. The partial nitration of cotton is accomplished by careful control of the temperature, the concentration of acid, and the length of time of the action. The nitrated cotton resembles the original cotton in its general appearance. In the process of manufacture it is washed free from acid and finally dried by whirling in a centrifuge. After this treatment it still contains considerable water and in this form is not explosive. The water is usually replaced by soaking in denatured alcohol and the material is again centrifuged. It is shipped without danger when it is moist with alcohol.

**Smokeless Powder.** When a mixture of gun cotton and the lower nitrates is treated with alcohol and ether, or certain other mixtures of organic solvents, it swells into a jellylike mass. This can be rolled into strips or cords of material which when dry have the consistency of dry gelatine. In the manufacture of smokeless powder, nitrated cotton is "gelatinized" in this way and molded into various shapes and sizes. When ignited in the open in small quantities, smokeless powder burns without exploding. The process is explosive, however, when the material is confined. Unlike black powder, there is no solid residue and therefore no smoke. The decomposition which evolves much heat may be represented by the following reaction:



**Celluloid and Lacquer Paints.** Celluloid is manufactured by gelatinizing pyroxylin with alcohol and heating it with camphor. The product may be molded into a variety of shapes by heating to about 100°. At room temperature it is hard and somewhat brittle. As would be expected from its close relationship to smokeless powder, it is very flammable.

Pyroxylin dissolves in a mixture of ether and alcohol, and the solution is known as **collodion**. A dilute collodion solution is often used as a *liquid court plaster*, since the solvent readily evaporates, leaving a thin film of transparent water-proof material. This material may be regarded as the forerunner of the **lacquer paints** which are widely used in the automobile industry. The development of these new lacquers has been made possible by the cheap production of the higher alcohols (p. 19) and by the discovery of a method of modifying pyroxylin.

Collodion would not be satisfactory as a lacquer for two reasons. In the first place, solutions of it which contain sufficient material to give a thick film on evaporation are extremely viscous. In the second place, the evaporation

of the low-boiling solvent is so rapid that the surface is cooled, and on a moist day water condenses, forming spots. The difficulty in regard to the viscosity is now avoided by heating the lower nitrates of cotton in slightly alkaline solution for a considerable time. This modified pyroxylin is very soluble in mixtures of various organic solvents, and the solutions are "thin" enough to flow freely on a brush or in an air spray.

Butyl acetate (b.p. 127°) is a solvent which does not evaporate too rapidly and is now a cheap material available in large quantities. It is blended with a great variety of other liquids, including hydrocarbons. Various gums, resins, and very high-boiling materials known as plasticizers are also incorporated in the lacquers. This lacquer industry has not only provided an outlet for butyl alcohol, which was originally a by-product of the preparation of acetone, but has stimulated the preparation of a variety of aliphatic compounds which may be used as solvents.

**Artificial Silk.** The essential difference between the appearance of silk and cotton goods is due to the mechanical structure of the fibers. Silk fibers are long, continuous, smooth tubes, whereas cotton fibers are relatively short and irregular. Silk is a protein (Chap. XXXI), but this is of little significance. The production of artificial silk from cotton is merely a matter of changing the mechanical structure of the carbohydrate fiber. This may be done by a variety of methods which are based on the same principle. A solution of cellulose or some cellulose derivative is forced through a very fine hole in such a manner that a continuous thread of solid material is formed. These almost invisible threads are then twisted together and the larger thread woven into cloth which closely resembles silk in its luster. **Rayon** is a name which has been given to artificial silk prepared by certain processes.

The manufacture of artificial silk is a major industry today. During 1937 about 150 thousand tons of rayon were produced in the United States alone.

One of the common methods of preparing artificial silk is the so-called **viscose process**. In this the cellulose is treated with carbon disulfide and alkali which gives a cellulose xanthate in

which the group  $\text{—}\overset{\text{S}}{\underset{\text{||}}{\text{C}}}\text{—SNa}$  is joined to one or more hydroxyl groups (p. 270). This cellulose xanthate with a small amount of water forms a thick solution known as *viscose*. This may be converted into threads of cellulose by squirting through a fine orifice into a solution which removes the xanthate group. **Cellophane** is the trade name given to thin, transparent sheets of

regenerated cellulose prepared by forcing viscose through a narrow slot into the regenerating solution; it is rendered moisture-proof by coating with a transparent lacquer.

In another process for preparing artificial silk, the cotton is dissolved in Schweitzer's reagent, and this solution is forced through a capillary tube into an acid solution which precipitates the cellulose as a long, continuous fiber.

**Cellulose Acetate.** The cellulose esters of the organic acids can not be prepared by direct esterification. It is necessary to use the acid anhydride. By the action of acetic anhydride on cotton in the presence of a little acid, cellulose acetate can be prepared. It has the formula  $[C_{12}H_{14}O_4(OCOCH_3)_6]_n$ . It is soluble in several organic solvents, particularly the halogen derivatives of the aliphatic hydrocarbons. On partial hydrolysis the material becomes soluble in a wider variety of solvents. Material thus prepared is soluble in acetone, and can be obtained as a strong flexible film by evaporating the solvent. Unlike the cellulose nitrates, cellulose acetate burns with difficulty. For this reason moving picture films prepared from it may be used without the precautions against fire which are necessary with the ordinary films manufactured from cellulose nitrate. An artificial silk is also made from cellulose acetate. Large quantities of acetic anhydride are manufactured for the use of this industry (p. 93).

**Pectins and Gums.** The pectins occur with the hemicelluloses in the cell walls of plant tissue. They pass into a colloidal solution in hot water. Such solutions will set to a gel on cooking and the solidification of fruit jellies depends on the presence of pectin in the fruit. It is now extracted commercially and sold as a powder to be added in the preparation of fruit jellies.

The gums are secretion products of diseased or injured plant tissue. They are usually soluble in water or at least swell in water. They are used to a limited extent in pharmacy and in the preparation of food products. The commonest commercial gum is **gum arabic**, a product secreted by some species of acacias. Both the pectins and the gums yield on hydrolysis a mixture of aldohexoses and **hexuronic acids**. The latter are substances having the formula  $HOOC(CHOH)_4CHO$ , which can be prepared by the oxidation of the terminal  $CH_2OH$  of an aldohexose to the corresponding acid. The hexuronic acid most commonly encountered in the plant world is **galacturonic acid** which corresponds to galactose.

It is very interesting to note that certain bacteria, in particular the pneumococci, form substances resembling the plant gums or hemi-celluloses. These carbohydrate materials form a protective capsule around the bacterium, and protect it against the engulfing action of the white blood cells.

### QUESTIONS AND PROBLEMS

1. Classify the carbohydrates and state the characteristics of each class.
2. In what respects are the aldohexoses and ketohexoses similar to each other and to simple aldehydes? In what respects do the three classes of compounds differ? (Write equations to illustrate the reactions which you may mention in answering this question.)
3. Outline the evidence which indicates that glucose is a straight chain penta-hydroxy aldehyde. Why has this simple formula been modified?
4. By what chemical tests could you distinguish between an aqueous solution of glucose and of sucrose?
5. Explain why phenylhydrazine is of importance in sugar chemistry. Write equations illustrating its use.
6. What chemical reactions of cellulose afford some evidence as to its structure?
7. (a) Outline two methods of preparing artificial silk. (b) How would you distinguish rayon from real silk?
8. Describe the manufacture of pyroxylin and indicate its many uses.
9. Trace the fate of sucrose when taken into the body as food and eventually utilized as a source of muscular energy.
10. Write structural formulas for the following: a hexuronic acid, a portion of the cellulose molecule, maltose, gluconic acid, sorbitol, ethyl glucoside, an osone, a portion of a cellulose xanthate molecule.
11. With the aid of equations show how the following transformations may be accomplished: (a) an aldopentose to an aldohexose; (b) an aldopentose to an aldotetrose (four carbon sugar); (c) an aldose to a ketose.
12. Write the stereochemical formulas for *d*-glucose and *d*-mannose (in open chain form). Write the stereochemical formula (open chain) for the aldopentose you would obtain by degradation of each of these sugars.
13. A naturally occurring glycoside on hydrolysis with acids yields an alcohol ROH and a molecule of glucose. How would you determine the configuration of the glycoside link and the size of the ring in this glucoside?
14. If from a certain methylated pentose one obtains on oxidation, a trimethoxy glutaric acid, what does this prove as to the structure of the original sugar?
15. Devise a synthesis of ascorbic acid which starts with an aldopentose of the proper configuration (*l*-xylose) and employs the reactions given in this chapter.
16. Compare the behavior of dihydroxy acetone and glyceric aldehyde with the aldo and keto hexoses.

## CHAPTER XVIII

### THE HYDROCARBONS FROM COAL TAR

**Cyclic Compounds.** In the preceding chapters we have considered for the most part compounds in which the carbon atoms were arranged in an open chain. In only a few instances, such as the cyclic anhydrides, have we encountered a substance whose structural formula contained a ring of atoms. The open chain compounds are known as **aliphatic compounds** (fatty compounds). This name arose from the fact that the fatty acids (derived from the fats) are representatives of this class of substances.

In addition to these open chain or aliphatic compounds a great variety of substances are known in which some of the atoms are combined in the form of a ring. These **cyclic compounds** are divided into two classes, depending on whether or not the ring is composed entirely of atoms of the same kind. The **homocyclic compounds** contain only carbon atoms in the ring, while the **heterocyclic compounds** have atoms of other elements in the ring. The homocyclic compounds are for convenience further divided into two groups, namely, the **alicyclic compounds**, which resemble closely the aliphatic compounds, and the **aromatic compounds**, a group of substances containing a ring with a peculiar type of unsaturation. We shall consider at some length certain of these aromatic compounds in the next few chapters, since in both the scientific and industrial development of organic chemistry this class of substances has played a very important role.

**The Development of Aromatic Chemistry.** Certain hydrocarbons found in coal tar, notably benzene,  $C_6H_6$ , contains an aromatic ring. The chemistry of these hydrocarbons and the substances which can be prepared from them is called **aromatic chemistry**. The chemist's interest in aromatic chemistry has been connected with the industrial development of this subject during the last 60 years. The fact that certain substances can be readily and cheaply obtained from coal tar early led to their extensive study with a

view to obtaining from them products of commercial importance. The efforts of the early investigators were richly rewarded as a great variety of dyestuffs, drugs, flavors and perfumes, photographic developers, and explosives were discovered. All these could be prepared from coal tar by relatively simple procedures. In order to appreciate and understand some of the triumphs of the organic chemist in this truly remarkable development we must acquaint ourselves with the general properties and behavior of that peculiar group of aromatic compounds which are found in coal tar.

**The Refining of Coal Tar.** The coal tar dye industry may be considered in a sense as a by-product of the steel industry. The distillation of coal yields coke, gas, ammonia, and coal tar. Coke

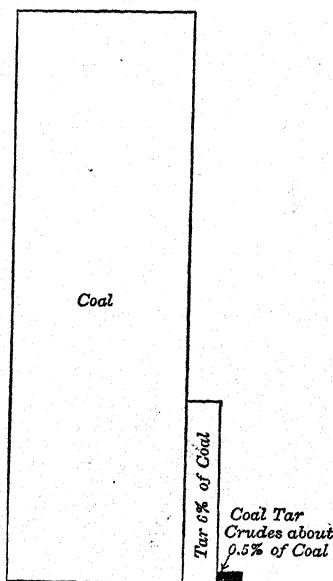
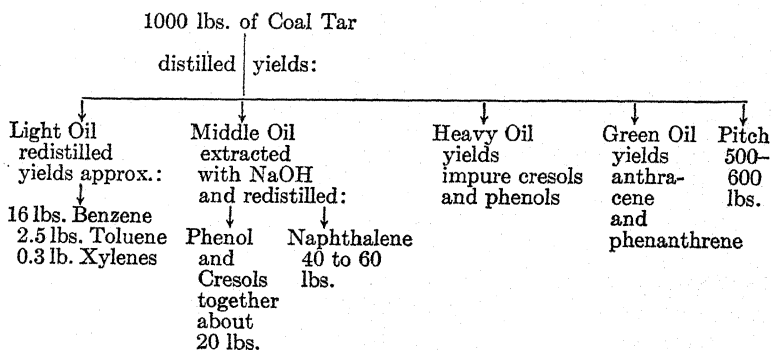


Fig. 26. Diagram illustrating the small yields of coal tar crudes from coal.

is essential in the winning of iron from its ores and would be prepared for this purpose whether or not the coal tar were collected and utilized. The diagram in Fig. 26 shows what a small fraction of the coal is obtained as tar and also what a small portion of the tar is finally obtained as coal tar crudes. In spite of this very low yield, benzene, toluene, and naphthalene are cheap

raw materials because an enormous amount of coal is each year converted into coke.

The refining of coal tar is done by distillation and by chemical treatment. The hydrocarbons are separated from each other by very efficient fractional distillation. Any basic nitrogenous material is removed by agitation with acid. Phenol,  $C_6H_5OH$ , and the cresols,  $CH_3C_6H_4OH$ , are weakly acidic compounds and are separated by shaking with sodium hydroxide solution. They pass into the aqueous layer and may then be obtained by acidification. The bulk of the tar is left as a black mass of pitch of unknown composition. It is used for roofing and for roads. The following diagram outlines the important steps:



**Coal Tar Crudes.** A number of substances may be obtained in a pure condition by the careful distillation of the light oil and

THE COAL TAR CRUDES

NAME	FORMULA	BOILING POINT	MELTING POINT	SOLUBILITY
Benzene	$C_6H_6$	80°	+ 6°	All insoluble in water
Toluene	$C_6H_5CH_3$	111°	- 95°	
<i>o</i> -Xylene	$C_6H_4(CH_3)_2$	144°	- 27°	
<i>m</i> -Xylene	$C_6H_4(CH_3)_2$	139°	- 54°	
<i>p</i> -Xylene	$C_6H_4(CH_3)_2$	138°	+ 13°	
Naphthalene	$C_{10}H_8$	218°	+ 80°	
Anthracene	$C_{14}H_{10}$	342°	+218°	
Phenanthrene	$C_{14}H_{10}$	340°	+101°	

middle oil. For this purpose a still is employed which is equipped with a very efficient fractionating column. Those compounds

which form a starting point for the synthesis of dyes, drugs, and explosives are called coal tar crudes. The eight hydrocarbons given in the table on page 325 may be listed as being the most important coal tar crudes.

### BENZENE

The simplest of the aromatic compounds is benzene,  $C_6H_6$ . By studying this one substance we shall learn a great deal about the characteristics of the entire class. Benzene (sometimes called benzol) was discovered in 1825 by Faraday.<sup>1</sup> He obtained it by fractional distillation of an oil which was a by-product of the manufacture of illuminating gas from whale oil. Twenty years later, the substance was isolated from coal tar and its chemical investigation continued by A. W. Hofmann.<sup>2</sup>

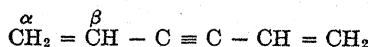
**Structure of Benzene.** The analysis and molecular weight of benzene correspond to the formula  $C_6H_6$ ; it is thus a member of a series of hydrocarbons with the general formula  $C_nH_{2n-6}$ . Although the formula suggests that it is a highly unsaturated substance, it is very different indeed from an open chain unsaturated hydrocarbon. *It reacts neither with bromine water nor potassium permanganate solution.* These two reagents, as we have seen, invariably react with aliphatic hydrocarbons having one or more double linkages.

The failure of an apparently highly unsaturated hydrocarbon to enter into addition reactions is indeed surprising. But even more interesting and significant facts have been disclosed by a study of the products formed by replacing one hydrogen atom of benzene by another atom or group. All methods of preparing a compound with one such atom or group (a monosubstitution product) have yielded *only one substance*. For example, one and only one bromobenzene,  $C_6H_5Br$ , has ever been prepared. Many different methods have been employed which would have yielded isomeric bromobenzenes if such were possible. It is evident that in an open chain compound such as represented by the formula I, or in an

<sup>1</sup> Michael Faraday (1791-1867). Professor at the Royal Institution, London. First served as Sir Humphry Davy's assistant in the same laboratory. His researches on electricity and magnetism were of the greatest importance in the development of physics.

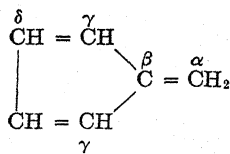
<sup>2</sup> August Wilhelm von Hofmann (1818-1892), (see p. 303, footnote). His study of the pure and applied chemistry and of aromatic compounds was so important that he may be considered the founder of the coal tar dye industry.

unsymmetrical ring compound, several monosubstitution products  $C_6H_5X$ , must exist.



I

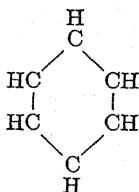
two isomers  $C_6H_5X$ ;  
substituent on  
 $\alpha$  or  $\beta$  atom



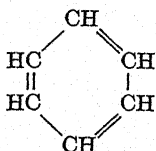
II

three isomers  $C_6H_5X$ ;  
substituent on atoms  
 $\alpha$ ,  $\gamma$  or  $\delta$

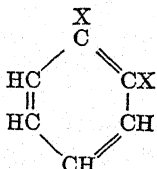
The only formula which is consistent with the fact that each hydrogen atom in benzene is equivalent to every other hydrogen atom is a formula having a symmetrical ring. The simplest formula meeting this condition is:



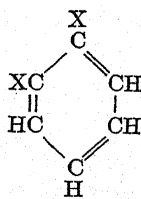
**The Benzene Problem.** The difficulties of taking care of the valences which are missing in the simple formula just written have troubled chemists ever since Kekulé in 1866 suggested the hexagonal formula for benzene. The simple expedient of writing alternate double linkages (formula I below), is difficult to reconcile with the fact that only one isomer having the substituents side by side (the ortho isomer) is known. According to formula I two isomers,  $C_6H_4X_2$ , II and III would be predicted.



I



II

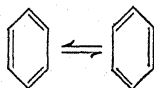


III

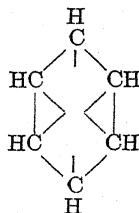
isomers of  $C_6H_4X_2$  predicted on the basis  
of formula I

To avoid this difficulty Kekulé suggested that the double link-

ages were continually oscillating back and forth between two positions. This may be represented as follows:

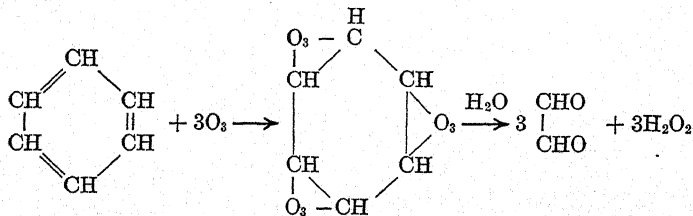


Baeyer suggested that the free valences were arranged in an entirely peculiar manner found only in aromatic compounds. This is called the centric formula:



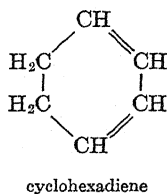
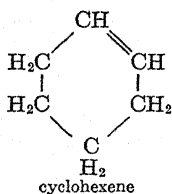
Various other formulas for benzene have been suggested which provide a possible solution of the problem, but no one formula has met with universal acceptance. The majority of chemists probably prefer an arrangement of alternate double and single linkages (formula I, above), and explain the non-existence of ortho isomers  $C_6H_4X_2$  by postulating a mobile shift of the double bonds.

Although benzene and its derivatives do not show the behavior typical of unsaturated compounds, there are a few addition reactions known. Thus, benzene slowly combines with chlorine in the sunlight to form benzene hexachloride,  $C_6H_6Cl_6$ . It can be catalytically reduced under special conditions to hexahydrobenzene,  $C_6H_{12}$  (p. 481). Benzene slowly reacts with ozone forming a triozone which on decomposition yields glyoxal:



This reaction might be cited as convincing evidence for the correctness of the formula with three double linkages.

**Aromatic and Unsaturated Alicyclic Hydrocarbons.** It is very interesting to compare benzene with the cyclic compounds which differ from it by only one or two pairs of hydrogen atoms. These substances are cyclohexene and cyclohexadiene.



These are alicyclic compounds and their reactions in every way resemble those of the corresponding open chain unsaturated substances, namely ethylene and butadiene. For example, both add bromine rapidly and are easily oxidized by potassium permanganate. The contrast between an unsaturated alicyclic compound and an aromatic hydrocarbon is evident.

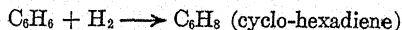
*The aromatic compounds are best defined as cyclic compounds with a peculiar degree of unsaturation.* From the experimental point of view this peculiar degree of unsaturation manifests itself on the one hand by the failure of the compound to show certain reactions of unsaturated compounds, and on the other by certain special types of reactions which we shall consider shortly. The contrast between aromatic and unsaturated compounds is not in all cases as striking as in benzene.

From the theoretical standpoint, the peculiar degree of unsaturation of aromatic compounds has presented a problem which is still unsettled. The best method of formulating the ring in benzene and related compounds continues to be a matter of discussion.

**Resonance of Benzene.** An inspection of the formulas on the top of page 328 shows that a ring containing an alternate series of double bonds differs in one important respect from any unsaturated aliphatic compound. It is possible to write formulas for possible isomers (*e.g.*, II and III) without shifting any atom whatsoever. If isomeric benzene derivatives of this type (corresponding to the double bond being in two different positions) could be isolated they would represent a different type of structural isomerism from any we have hitherto met. For in such a case, let it be carefully noted that the isomers would be identical in regard to the

position of all the atoms and only the position of the double bond would be different. Or expressed another way, the two isomers (if they existed) would only differ in the position of certain valency electrons (which the bonds represent). This is exactly the situation we have encountered in considering the structure of the guanidinium ion (p. 258). As we have already noted, it is a remarkable and significant fact that no two isomeric organic compounds have ever been isolated which differ only in the position of electrons. It is not hard to see why this should be since we have seen in connection with acetoacetic ester how easily one isomer is converted into another when only a hydrogen atom has to move. When no atom but merely electrons are involved in the shift it is not surprising that isomers do not exist. It is a further fact, already mentioned (p. 258), that whenever it is possible to write for a compound two isomeric formulas which differ only by the position of the bonds (no atoms being shifted) that compound is more stable and usually less reactive than would otherwise be expected. The explanation of this situation in terms of the newer electron theories of valency was considered in our discussion of the guanidinium ion (p. 259). This phenomenon of **resonance energy** and a shortening of the link. In the case at hand, it has been found that all six bonds in benzene are of the same length. The inter-nuclear distance is only 1.39A as compared with 1.54A for the C—C normal link and 1.34A for the C=C normal bond.

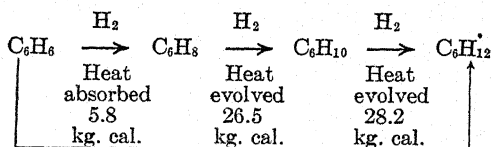
A consideration of the energy changes involved in the hydrogenation of benzene brings out the increased stability of this arrangement of atoms and also shows why benzene does not combine with such reagents as bromine. The heat evolved in the addition of pairs of hydrogen atoms to various unsaturated and aromatic compounds has been measured and the unique position of benzene and its relatives is conspicuous. Whereas in the addition of H<sub>2</sub> to substituted ethylenes or unsaturated alicyclic compounds such as cyclohexene, 28–30 kg. cal. of heat is evolved, the reaction



*absorbs* heat to the extent of about 6 kg. cal. (*i.e.*, is endothermic). In other words, the reaction under ordinary conditions of pressure runs to completion in the other direction — cyclohexadiene is unstable with respect to benzene and hydrogen. When cyclohexadiene is treated with a number of different catalysts benzene is formed and usually the hydrogen which is eliminated is used up in hydrogenating some of the original cyclohexadiene. The heat evolved in an addition reaction is an approximate measure of the affinity of the

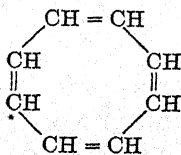
unsaturated compound for the reagent. The difference between 6 kg. cal. of heat *absorbed* and 28–30 kg. cal. of heat *evolved* in the hydrogenation of a simple double bond (a total of 34–36 kg. cal.) is a measure of the resonance energy of benzene.

It is clear from the facts just stated that benzene has so little affinity for one mole of hydrogen ( $H_2$ ) that it will not combine with it even in the presence of a catalyst at any ordinary pressure of hydrogen. (It can be calculated that a pressure of about  $10^{11}$  atm. of  $H_2$  would be necessary to make the reaction written above proceed from left to right to a point where 90 per cent of the benzene was hydrogenated.) A similar lack of affinity for such reagents as bromine and chlorine is the reason why benzene and its relatives do not show the usual reactions of unsaturated compounds. It should be remembered, however, that this lack of affinity applies only to the addition of one pair of atoms. In the hydrogenation of cyclohexadiene to cyclohexene 26.5 kg. cal. is evolved and in the transformation of cyclohexene to hexahydrobenzene (cyclohexane) 28.2 kg. cal. is liberated. Therefore, with a suitable catalyst it is possible to hydrogenate benzene completely without difficulty.

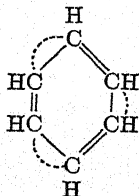


Over-all heat evolved 48.9 kg. cal.

**Thiele's Benzene Formula.** Another way of formulating benzene and its derivatives was suggested by Thiele. He pointed out that either phase of the Kekulé formula contained a conjugated system (p. 294) without terminal atoms. The residual affinity which he represented as being accumulated on the ends of the usual conjugated system was here imagined to be equally distributed over the six carbon atoms, and thus largely neutralized. The same line of reasoning leads to the conclusion that a compound with alternate double and single linkages in an eight-membered ring should not react as an unsaturated cyclic compound but as an aromatic hydrocarbon. Such a compound, known as cyclo-octatetraene, might be expected according to Thiele's theory to be as peculiar as benzene.



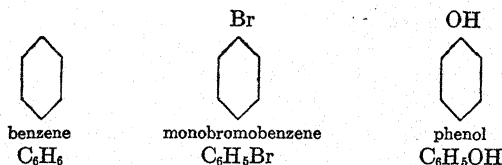
cyclo-octatetraene



Thiele's formula  
for benzene

Essentially the same conclusion would follow from the line of reasoning which emphasizes the possibility in benzene of writing two isomeric formulas differing only in the position of bonds (*i.e.*, a condition of resonance). Unfortunately, cyclo-octatetraene is very difficult to prepare and our knowledge concerning it is limited, but probably enough is known to make it safe to say that it combines with chlorine and bromine and even hydrobromic acid. This hydrocarbon has evidently much more affinity for one pair of atoms than benzene. Until some quantitative study of this compound is made, one can not say whether it stands nearer to a typical aromatic or to an unsaturated alicyclic compound. It is probably very significant that crystalline derivatives of benzene have been shown by X-ray analysis to have all the carbon atoms of the ring in a plane. This planar configuration of the benzene ring, and the peculiar symmetrical arrangement of the unsaturation are probably both responsible for the large resonance energy and the peculiarities which we have been discussing.

**Conventional Outline Formulas.** For many practical purposes it makes little difference how we dispose of the extra valences in benzene, and, therefore, a method of writing formulas has been adopted which leaves the problem entirely unanswered. Benzene is represented by a hexagon; neither the carbon atoms nor the hydrogen atoms are written. It is assumed that the group CH constitutes each corner. If a group or atom has replaced a hydrogen, this group or atom is written. The following examples will make this clear.

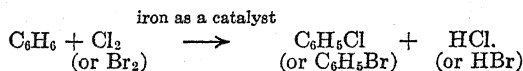


In the formulas written above, it is immaterial whether the bromine atom and hydroxyl group are written at the top, side, or bottom of the hexagon. The ring is symmetrical and every position is equivalent to every other.

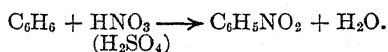
**Aromatic Properties.** The chemical properties which are characteristic of benzene and its derivatives are often spoken of as *aromatic properties*. These include: (a) resistance to oxidation; (b) acidic properties of the hydroxyl derivatives (to be discussed later); (c) failure to add reagents which usually add to the unsaturated compounds; (d) the ready substitution of hydrogen by other atoms or groups.

The last characteristic is of special interest and needs amplification. The characteristic substitution reactions are:

(1) *Halogenation*, the substitution of hydrogen by chlorine or bromine:

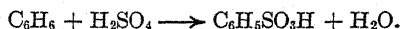


(2) *Nitration*, the substitution of hydrogen by the nitro group:

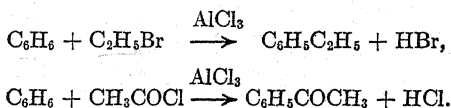


A mixture of concentrated nitric and sulfuric acids is used.

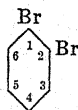
(3) *Sulfonation*, the substitution of hydrogen by the sulfonic acid group:



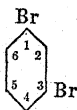
(4) *Friedel and Crafts*<sup>1</sup> *reaction*, the introduction of an alkyl or acyl group by means of the halide and aluminum chloride:



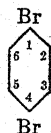
**Number of Substitution Products.** We have seen that it has been experimentally established that all the positions in the benzene ring are equivalent. There are only three isomers of a compound C<sub>6</sub>H<sub>4</sub>X<sub>2</sub>. The nomenclature of these isomers may be illustrated by the case of dibromobenzene, C<sub>6</sub>H<sub>4</sub>Br<sub>2</sub>.



ortho  
dibromobenzene  
or 1, 2-dibromo-  
benzene



meta  
dibromobenzene  
or 1, 3-dibromo-  
benzene

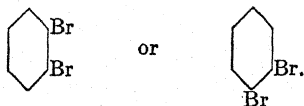


para  
dibromobenzene  
or 1, 4-dibromo-  
benzene

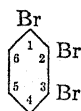
The terms, ortho, meta, and para should be noted. It is, of course,

<sup>1</sup> C. Friedel (1832-1899), a French chemist with whom the American J. M. Crafts (1839-1900) worked at the Sorbonne, Paris, in 1877. Crafts was Professor of Chemistry at the Massachusetts Institute of Technology.

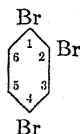
only the relative positions of the groups which is important, and the ortho compound, for example, may also be written:



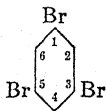
There are three isomers of a trisubstituted benzene of the formula  $C_6H_3X_3$ . Thus, there are three tribromobenzenes:



1, 2, 3-tribromobenzene  
(vicinal form)



1, 2, 4-tribromobenzene  
(asymmetric form)



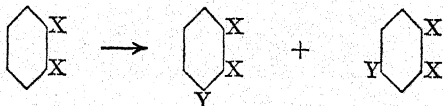
1, 3, 5-tribromobenzene  
(symmetric form)

**Nomenclature of Polysubstituted Benzenes.** The method of nomenclature which is used with benzene derivatives containing more than two groups involves the numbering of the ring as indicated above. The disubstitution products are also sometimes referred to in this way; thus, ortho dibromobenzene is 1, 2-dibromobenzene, and the para compound 1, 4-dibromobenzene.

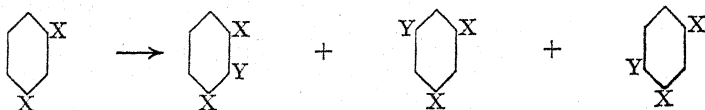
**Determination of Positions of Substituents.** Three and only three compounds with the formula  $C_6H_4Br_2$ , are known; the ortho, meta, and para isomers. The question now arises, how is it possible to decide which substance is ortho, which meta, and which para? A similar problem exists in regard to any benzene derivative with two or more substituents. The actual steps in determining the structure of aromatic compounds are complicated and often difficult, but the general principle involved is very simple. By understanding this principle, we shall become acquainted with the fundamental basis for all the formulas of aromatic compounds which will be presented in the following chapters.

The ortho, meta, and para isomers differ in regard to the number of trisubstitution products which it is possible to prepare from them. This is illustrated below:

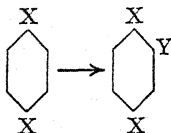
*Ortho Isomer, two possible trisubstitution products:*





*Meta Isomer, three possible trisubstitution products:*



*Para Isomer, only one trisubstitution product:*



It must be remembered in this connection that such formulas as  and  are the same though at first sight they

appear different. (In this case, the two may be superimposed by rotating through  $180^\circ$  and folding the paper.) With this in mind one can easily convince oneself of the correctness of the propositions stated above by a few moments with a pencil and paper.

Returning now to the specific case of the three isomeric dibromobenzenes, it is only necessary to take each isomer and determine the *maximum* number of substitution products  $C_6H_3Br_2Y$  which can be prepared from it (where Y may be the  $NO_2$  group, for example). The isomer which yields only one is the para, that yielding two is the ortho and the third which yields three is the meta. This has been done by methods many of which will be considered in the following chapters; the results have established the structure of the isomers once and for all. Similar procedures with other isomeric compounds have yielded similar results. This is known as the **absolute method** of determining the position of groups. It was first employed by Körner,<sup>1</sup> and one of the cases studied by him was that of the dibromobenzenes.

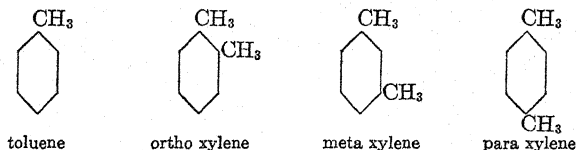
After the structure of a number of aromatic compounds had been established by the absolute method, it was possible to use these substances as points of reference in determining the structure of other compounds. For example, a certain dinitrobenzene,  $C_6H_4(NO_2)_2$ , can be transformed by a series of reactions (Chap. XXI) into the dibromobenzene which melts at  $87^\circ$ . The absolute

<sup>1</sup> Wilhelm (Guglielmo) Körner, 1839-1925, Professor at Milan.

method had previously shown that this particular dibromobenzene is the para isomer. Therefore, the dinitrobenzene, which could be transformed into it, was also the para isomer. Such methods are now employed in determining the structure of the new benzene derivatives which are from time to time prepared in the course of investigations of scientific or industrial problems.

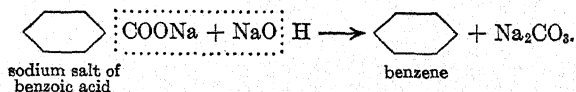
#### ALKYL DERIVATIVES OF BENZENE

The alkyl derivatives of benzene are very similar to the parent substance in their general behavior. Toluene,  $C_6H_5CH_3$ , and the isomeric xylenes are readily obtained from coal tar. We shall have many occasions to refer to toluene since it can be transformed into a variety of important substances. The structure of toluene and of the three isomeric xylenes are as follows:



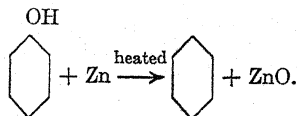
The boiling points of the three isomeric xylenes lie so near together that it is a difficult matter to separate the one from the other. Commercial xylene is a mixture of all three. We shall see in general that the separation of a mixture of ortho, meta, and para isomers is a difficult matter. It can be accomplished only by very efficient fractional distillation or by repeated crystallization if the substances are solids.

**Methods of Preparing Aromatic Hydrocarbons.** Although benzene, toluene, and the xylenes are obtained from coal tar, it is important to have general methods of preparing aromatic hydrocarbons. Some of these are very similar to the methods used for preparing aliphatic hydrocarbons. For example, the sodium salts of aromatic acids on heating with sodium hydroxide yield the corresponding hydrocarbon:

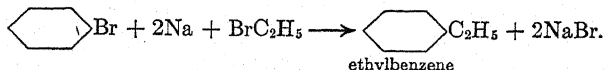


The hydroxyl derivatives of aromatic hydrocarbons may be reduced to the hydrocarbon by distillation with zinc dust. This

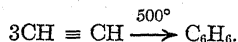
method has been of value in determining the structure of certain hydroxyl compounds which occur in nature (alizarin, p. 556):



The introduction of alkyl groups into the aromatic ring (or nucleus as it is often called) may be accomplished by the Friedel and Crafts reaction previously mentioned (p. 333) or by the Wurtz-Fittig reaction. The latter reaction is illustrated by the preparation of ethylbenzene from bromobenzene, ethyl bromide, and sodium:



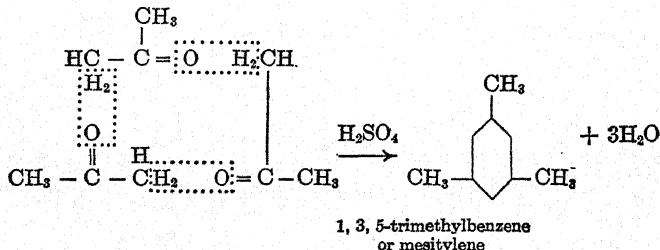
The preparation of aromatic hydrocarbons from aliphatic compounds is possible but, with a few exceptions, rarely employed. Acetylene at a high temperature polymerizes to benzene:



Aromatic hydrocarbons are also obtained from paraffin hydrocarbons by pyrolysis. High temperature, pressure, and special catalysts are essential. Thus, when *n*-octane is subjected to pyrolysis, ortho xylene is one of the chief products.

In the cracking of petroleum fractions, the product becomes richer in aromatic hydrocarbons. As we have seen (p. 52), the presence of small amounts of these hydrocarbons in gasoline is desirable. Natural gas and the gases obtained from the cracking process can also be pyrolyzed to aromatic hydrocarbons. In some localities the production of these hydrocarbons from cracked gases is an industrial reality.

The symmetrical trimethylbenzene, known as *mesitylene*, is always prepared by the action of sulfuric acid on acetone.



Other condensation reactions of acetone which take place in the presence of acid catalysts and involve the elimination of water yield unsaturated ketones (p. 291), as for example, mesityl oxide,  $(\text{CH}_3)_2\text{C} = \text{CHCOCH}_3$ , and phorone,  $(\text{CH}_3)_2\text{C} = \text{CHCOCH} = \text{C}(\text{CH}_3)_2$ . The heat evolved in these condensations is relatively slight and corresponds to a reversible reaction in which measurable amounts of reactants and products are present at equilibrium. In the case of the formation of mesitylene, however, it can be estimated from energy relationships that the heat evolved is large and if equilibrium conditions could be realized, the concentration of acetone would be much too small to be measured (far less than .0001 per cent). The greater stability of the aromatic ring and the tendency of reactions producing this ring to go to practical completion is evident from this example.

**Higher Homologs of Toluene.** The physical properties of some of the simpler alkyl derivatives of benzene are given in the accompanying table.

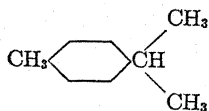
PHYSICAL PROPERTIES OF SOME ALKYL DERIVATIVES  
OF BENZENE

NAME	FORMULA	MELT- ING POINT	BOIL- ING POINT	DEN- SITY AT 20°
Toluene	$\text{C}_6\text{H}_5\text{CH}_3$	- 92.4°	111°	.865
Ortho xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	- 28°	142°	.863
Meta xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	- 54°	140°	.865
Para xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	+ 15°	138°	.863
Ethylbenzene	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5$	- 94°	135°	.876
Propylbenzene	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3$		150°	
Isopropylbenzene (Cumene)	$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)_2$		169°	
Pseudocumene	$\text{C}_6\text{H}_3(\text{CH}_3)_{3-1, 2, 4}$	- 45°	165°	
Mesitylene	$\text{C}_6\text{H}_3(\text{CH}_3)_{3-1, 3, 5}$	- 53°	165°	
1, 2, 3, 5-tetramethylbenzene	$\text{C}_6\text{H}_2(\text{CH}_3)_4$	below 0°	195°	
1, 2, 3, 4-tetramethylbenzene	$\text{C}_6\text{H}_2(\text{CH}_3)_4$	- 4°	204°	
1, 2, 4, 5-tetramethylbenzene (Durene)	$\text{C}_6\text{H}_2(\text{CH}_3)_4$	+ 79-80°	194°	
1, 2, 3, 4, 5-pentamethylbenzene	$\text{C}_6\text{H}(\text{CH}_3)_5$	+ 53°	231°	
Hexamethylbenzene	$\text{C}_6(\text{CH}_3)_6$	+ 169°	264°	

In general, both the boiling point and melting point increase with increasing molecular weight. The effect of symmetry on the melting point (but *not* the boiling point) is evident in the high melting points of *durene*, 1, 2, 4, 5-tetramethylbenzene (m.p. 80°), and hexamethylbenzene (m.p. 169°). These compounds together with the pentamethyl compound are formed by the

prolonged action of methyl chloride on benzene (Friedel-Crafts reaction).

**Cymene** (or para cymene), 1-methyl-4-isopropylbenzene,

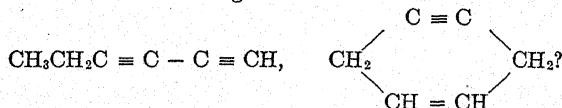


is closely related to a number of the terpenes which are considered in Chap. XXVII. Many terpenes may be converted into this hydrocarbon (p. 489). It occurs in a variety of essential oils. The structure of cymene was established by synthesis early in the development of the theory of structure. This established the nature of the carbon skeleton in those terpenes which could be transformed into it.

**Nomenclature of Aryl Groups.** Just as we have names for the alkyl groups, so it is convenient to have names for the groups corresponding to an aromatic radical — aryl groups. The aryl group,  $C_6H_5-$ , is known as the phenyl group. The name originated from the fact that the corresponding hydroxyl compound,  $C_6H_5OH$ , is known as phenol. It must be noted that in this case the name of the aryl group does *not* suggest the name of the corresponding hydrocarbon. However, in the case of the aryl groups corresponding to the alkyl derivatives of benzene, the nomenclature usually follows that of the hydrocarbon. Thus,  $CH_3C_6H_4-$  is the tolyl group (ortho, para or meta),  $(CH_3)_2C_6H_3-$ , the xylyl group, and  $(CH_3)_3C_6H_2-$ , the mesityl group. The group,  $CH_3C_6H_4-$ , is also sometimes called the cresyl group, the name being derived from that of the hydroxyl compound,  $(CH_3C_6H_4OH)$ , cresol.

### QUESTIONS AND PROBLEMS

1. What is the evidence for the cyclic structure of benzene? What experimental facts exclude the following formulas:



2. Compare the chemical behavior of ethylene, acetylene, benzene, cyclohexene.

3. Write structural formulas for all the isomers of the following derivatives of benzene:  $C_6H_4(CH_3)_2$ ,  $C_6H_3Br_3$ ,  $C_6H_4(OH)_2$ .

4. Write structural formulas for: para dimethylbenzene, ortho xylene, meta dibromobenzene, 1, 2, 5-trichlorobenzene, mesitylene, para cymene.
5. Describe briefly the steps in the refining of coal tar, naming the important "coal tar crudes."
6. What products would you expect from the ozonolysis of ortho xylene?
7. Write equations showing the action of concentrated sulfuric acid on: benzene, ethylene, ethyl alcohol.
8. What method is available for preparing an aromatic hydrocarbon from an aromatic acid? From a phenol?
9. How would you suggest preparing *n*-propylbenzene from coal tar and aliphatic compounds?
10. An aromatic compound A,  $C_8H_{10}O$ , when distilled with zinc dust gave an aromatic hydrocarbon B,  $C_8H_{10}$ . When B was nitrated, one trisubstitution product was obtained. What is the structure of A?
11. Discuss the absolute method of orientation in the benzene ring. Using the three isomeric trisubstitution products of benzene, indicate by this method how the structure of each isomer may be determined.

## CHAPTER XIX

### ARYL HALIDES, SULFONIC ACIDS, AND PHENOLS

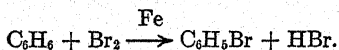
#### ARYL HALIDES

One of the characteristic reactions of aromatic compounds is the replacement of a hydrogen atom on the ring by chlorine or bromine. The resulting compounds are **aryl halides**. Unlike the alkyl halides, the simple aryl halides are almost never prepared from the corresponding hydroxyl compounds. They are usually prepared from the hydrocarbons. The following table lists some of the more important aryl halides; they are all insoluble in water.

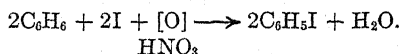
#### CHLORO, BROMO, AND IODO DERIVATIVES OF BENZENE AND TOLUENE

NAME	FORMULA	BOILING POINT	MELTING POINT
Chlorobenzene	$C_6H_5Cl$	132°	- 45°
Bromobenzene	$C_6H_5Br$	156°	- 31°
Iodobenzene	$C_6H_5I$	189°	- 31°
<i>o</i> -Chlorotoluene	$CH_3C_6H_4Cl(o)$	159°	- 35°
<i>m</i> -Chlorotoluene	$CH_3C_6H_4Cl(m)$	162°	- 48°
<i>p</i> -Chlorotoluene	$CH_3C_6H_4Cl(p)$	163°	+ 8°
<i>o</i> -Bromotoluene	$CH_3C_6H_4Br(o)$	182°	- 28°
<i>m</i> -Bromotoluene	$CH_3C_6H_4Br(m)$	184°	- 40°
<i>p</i> -Bromotoluene	$CH_3C_6H_4Br(p)$	184°	+ 28°
<i>o</i> -Iodotoluene	$CH_3C_6H_4I(o)$	211°	—
<i>m</i> -Iodotoluene	$CH_3C_6H_4I(m)$	204°	—
<i>p</i> -Iodotoluene	$CH_3C_6H_4I(p)$	212°	35°

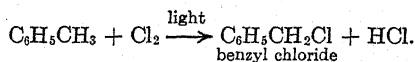
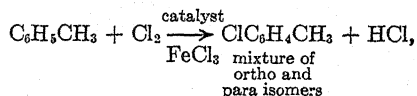
**Chlorobenzene and Bromobenzene.** These two substances may be taken as typical representatives of the aryl halides. They are prepared by the action of chlorine or bromine on warm benzene in the presence of some catalyst. Iron is almost always the catalyst employed.



The product is purified by distillation. In addition to the monohalogen compound, some dichloro- or dibrombenzene is also formed. Unlike bromine and chlorine, iodine, by itself, does not directly replace a hydrogen atom attached to an aromatic ring. Iodobenzene, however, can be made by the action of iodine and boiling nitric acid on benzene.

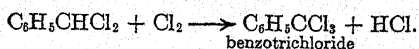
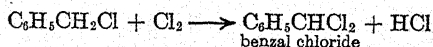


**Halogenation of Alkyl Derivatives of Benzene.** The alkyl derivatives of benzene such as toluene and ethylbenzene may react in two different ways when treated with chlorine or bromine. A hydrogen atom of the nucleus or a hydrogen atom of the alkyl group (the "side chain") may be replaced. The nuclear halogenation is accelerated by such catalysts as metallic iron or ferric salts; the introduction of a halogen atom into the side chain is favored by strong light and high temperature.



It will be noticed that the product of the side-chain chlorination, **benzyl chloride** (b.p. 179°), does not contain the halogen atom directly attached to the aromatic ring. It is, therefore, not an aryl halide like ortho and para chlorotoluene but an alkyl halide (methyl chloride) in which one hydrogen atom has been replaced by an aromatic group ( $\text{C}_6\text{H}_5$ ).

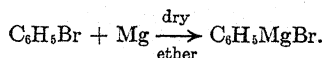
The chlorination of the side chain of toluene proceeds further to give **benzal chloride** (b.p. 207°),  $\text{C}_6\text{H}_5\text{CHCl}_2$ , and finally **benzotrichloride** (b.p. 213°),  $\text{C}_6\text{H}_5\text{CCl}_3$ . Unlike the chlorination of methane (p. 50), the side-chain reaction of toluene with chlorine can be controlled so that any one of the three chlorination products can be obtained in a good yield.



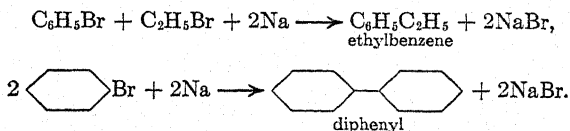
**Dichlorobenzenes.** On chlorination of chlorobenzene in the presence of iron three disubstitution products are obtained: ortho, 39 per cent (m.p.  $-17.6^{\circ}$ , b.p.  $179^{\circ}$ ); meta, 5 per cent (m.p.  $-24.8^{\circ}$ , b.p.  $173^{\circ}$ ); para, 55 per cent (m.p.  $56^{\circ}$ , b.p.  $174^{\circ}$ ). Paradichlorobenzene is used extensively as a moth and caterpillar repellant.

**Chemical Behavior of Aryl Halides.** In comparison with the alkyl halides, the aryl halides are very unreactive; for example, they do not react with potassium cyanide, silver hydroxide, or, under the usual conditions employed in the laboratory, with sodium hydroxide or ammonia. When heated under pressure to  $200^{\circ}$ – $300^{\circ}$  with these last two reagents and copper salts, the halogen atom may be replaced by the OH and  $\text{NH}_2$  groups respectively.

Aryl halides react with magnesium to form a Grignard reagent which is similar to the aliphatic Grignard reagents:



Aryl halides react with metallic sodium in the Wurtz-Fittig reaction considered in the last chapter. If no alkyl halide is employed two molecules of the aryl halide join together:

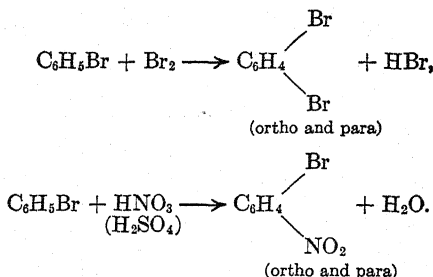


It is interesting to recall that the halogen derivatives of unsaturated aliphatic hydrocarbons, such as vinyl bromide,  $\text{CH}_2 = \text{CHBr}$ , are also unreactive (p. 278) and, in this respect, resemble the aryl halides. A consideration of the formula for benzene suggests a reason for this striking analogy. A halogen atom directly attached to an unsaturated atom is unreactive; the nuclear atoms in benzene are unsaturated (however, one chooses to write the benzene formula) and hence the aryl halides do not readily enter into metathetical reactions.

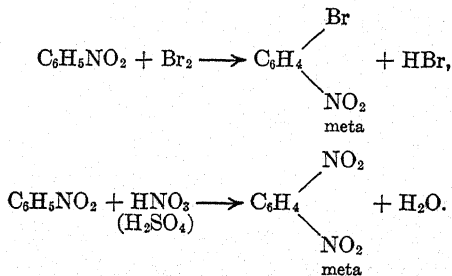
**Formation of Ortho, Meta, and Para Isomers.** In the preparation of the disubstitution products of benzene, three isomers are possible. For example, the further bromination of bromobenzene might yield the ortho or the meta or the para isomer. As a

matter of fact, the product is a mixture of the ortho and para compounds. On the other hand, the bromination of nitrobenzene,  $\text{C}_6\text{H}_5\text{NO}_2$ , yields the meta bromonitrobenzene. Some rules for predicting the isomers are obviously needed.

**The Directive Influence of Substituents.** An exhaustive study of the preparation of disubstituted benzenes has led to *two important generalizations*. These are subject to certain reservations but are nevertheless of great value as an approximate guide in predicting the course of substitution reactions. The first generalization is as follows: *the position of the entering group is determined by the nature of the atom or group already present* and is independent of the nature of the entering group. For example, the bromination of bromobenzene yields a mixture of the ortho and para compounds, and the nitration of bromobenzene proceeds in the same way:



On the other hand, the nitration of nitrobenzene yields only the meta compound, and similarly the bromination of nitrobenzene yields only meta bromonitrobenzene.



**Rules of Orientation.** It will be seen from the above example that the directing influences of the bromine atom and the nitro group are different. One causes the formation of a mixture of

ortho and para isomers, the other only of the meta compound. It has been found that all the atoms or groups which are common substituents in the benzene ring may be divided into two categories according to whether they have a directive influence like that of the bromine atom or like that of the nitro group. This is the second great generalization in regard to substitution in aromatic compounds.

A list of the groups is given below:

**Class I.** (Directs the entering group into the ortho and para position.)  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{CH}_3$  and other alkyl groups,  $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{NH}_2$  (with one very important exception),  $-\text{NHCOCH}_3$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{COOH}$ .

**Class II.** (Directs the entering group into the meta position.)  $-\text{SO}_3\text{H}$ ,  $-\text{NO}_2$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CHO}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{COR}$ ,  $\text{NH}_3^+$ ,  $-\text{NR}_3^+$ .

Those atoms and groups in Class I are spoken of as **ortho and para orienting atoms or groups**; those in Class II as **meta orienting groups**. It will be convenient to remember that all those groups which contain a double linkage *connected to the first atom* fall in Class II as do those which carry a positive charge on the atom directly attached to the ring. In general, the introduction of a second substituent into a molecule is easier (*i.e.*, proceeds more rapidly at a lower temperature) if the substituent already present belongs to Class I but more difficult when the substituent present is of Class II.

**Limitations of the Rules.** Several important exceptions to these rules of orientation will be noted later, even in this elementary presentation of the subject; if a greater number of aromatic compounds were considered, the exceptions would be more numerous. Not only are there certain cases where the facts are exactly contrary to the simple rules of orientation, but, in general, the *rule only predicts the major product of the reaction*. There is, almost always, at least a few per cent of the other isomers formed. In spite of these limitations, the rules of orientation are of invaluable assistance in the practical matter of devising syntheses of aromatic compounds with several groups. We shall repeatedly refer to them.

**Factors Influencing the Proportions of Isomers.** We have just seen that the major course of a substitution reaction is determined by the nature of the group already attached to the ring. Relatively minor variations in the propor-

tions of the isomers, however, are affected by the nature of the entering group. For example, bromobenzene, on chlorination, bromination, and nitration yields predominantly a mixture of ortho and para isomers in each case as predicted by the general rules. The small amount of meta isomer produced varies, however, from a minimum of 0.3 per cent in the nitration to a maximum of 6 per cent in the chlorination (using iron as a catalyst). The variations in the ratio of para to ortho isomer are shown by the following tabulation:

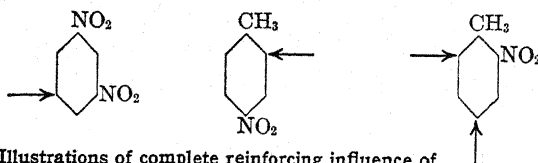
RATIO OF PARA TO ORTHO ISOMER FORMED ON INTRODUCING A SECOND GROUP INTO BROMOBENZENE

Second group:	Br	Cl	NO <sub>2</sub>
Ratio of para to ortho isomer:	6.4	1.2	1.7

The conditions under which the reaction is carried out also often have an important effect on the proportion of isomers. For example, the chlorination of chlorobenzene using aluminum chloride as a catalyst yields more than twice as much para as ortho compound (66 : 30); with ferric chloride the two isomers are formed in more nearly equal amounts (55 : 40). The temperature may affect the relative amounts of isomers. This is particularly true of nitration and sulfonation. For example, the sulfonation of toluene at 0° yields the ortho and para isomers in approximately equal amounts with about 4 per cent of the meta isomer; at 100°, the three toluene sulfonic acids are formed in the proportions 73 of para to 17 of ortho to 10 of meta.

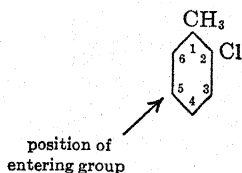
**Introduction of a Third Substituent.** The rules of orientation are not confined to the formation of disubstitution products. With certain qualifications they are also applicable to the prediction of the position taken by an entering group in the formation of higher substitution products. Experiment has shown that the effect of two or more groups may be predicted from a knowledge of the orienting influence of each group alone and an estimate of the relative orienting strength of the group. The common groups are usually given in the following order, the first having the strongest influence: (A) Class I, OH and NH<sub>2</sub> > CH<sub>3</sub>CONH > Cl > I > Br > CH<sub>3</sub>; (B) Class II, NO<sub>2</sub> > COOH. > SO<sub>3</sub>H. A few illustrations of the application of these principles will indicate the general idea. The extension of the principles to the many different special cases that arise is an easy matter. If the orienting influences of both groups completely reinforce each other, the case is very simple. For example, two meta orienting groups in the meta position will cause the third substituent to take the 5 position. In such a case, the amount of the ortho isomer is very small indeed. A similar case is one in which an ortho and para orienting group is

para or ortho to a meta orienting group. Here again both influences work for the substitution in the same positions.



Illustrations of complete reinforcing influence of both groups (the position of the entering group is shown by the arrow).

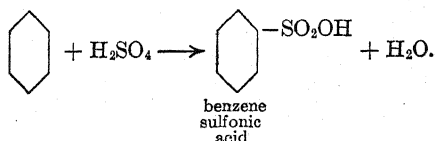
If the influence of the two groups is directed to different atoms then the possibility is present of forming a number of isomers. For example, in a molecule in which two similar groups (of either class) are in the ortho or para position to each other, the directive influences are such that every unoccupied position in the benzene nucleus may be substituted. However, experiments have borne out the fact that the position of the substitution is then determined by the relative influence of the two groups. For example, in the nitration of ortho chlorotoluene the entering group takes the position para to the chlorine atom whose orienting influence is greater than the methyl group.



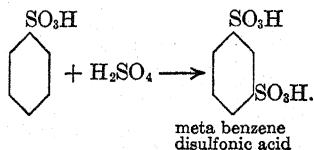
### ARYL SULFONIC ACIDS

**Aryl Sulfonic Acids.** One of the characteristic reactions of aromatic compounds mentioned in the previous chapter is sulfonation. The product of this reaction is an aryl sulfonic acid, which is usually isolated as a salt. The aryl sulfonic acids are of great importance in the preparation of other compounds since the sulfonic acid group may be replaced by other groups. The sulfonic acid group is also often introduced into a molecule in order to make the compound soluble in water. The aryl sulfonic acids of low molecular weight and most of their salts are soluble in water. Even some aromatic hydrocarbons of very complex structure and high molecular weight may be changed into water-soluble products by the introduction of a number of sulfonic acid groups.

**Sulfonation of Aromatic Hydrocarbons.** The sulfonation of benzene is typical of the procedure employed in the preparation of an aryl sulfonic acid and the isolation of the sodium salt. In the usual procedure benzene is agitated with a large excess of sulfuric acid kept somewhat above room temperature.



The rate of the reaction depends on the concentration of the sulfuric acid and the temperature. The water formed in the process decreases the speed by diluting the acid. If sulfur trioxide is present (as is the case in *fuming* sulfuric acid), it unites with the water and keeps the reagent anhydrous throughout the reaction. The higher the temperature and the more sulfur trioxide in the acid, the more rapid is the sulfonation. One, two, or three sulfonic acid groups may be introduced into benzene depending on the conditions of the reaction. There is no difficulty in controlling the process so that either the mono- or the disulfonic acid is the sole product.

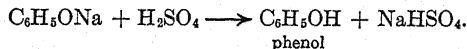
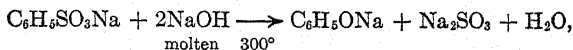


The aryl sulfonic acids are non-volatile solids which are soluble in water and insoluble in most organic solvents. Because of this, the isolation of the sulfonic acids from the reaction mixture which contains a large amount of sulfuric acid requires a rather special method. Advantage is taken of the fact that the calcium, barium, or lead salts of sulfonic acids are soluble in water. Hence, the reaction mixture is first diluted with water, neutralized with lime (a process known in industry as **liming out**), and filtered. The filtrate of this mixture contains the calcium salt. The calcium salts of sulfonic acid are readily converted to sodium salts by treatment with sodium carbonate. In some cases the sodium salts of sulfonic acids may be precipitated by saturating the solution with sodium chloride.

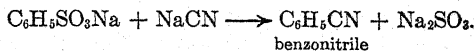
**Isolation and Properties of Free Sulfonic Acids.** The free aromatic sulfonic acids are rarely isolated, and are very little employed as such. They may be obtained from the calcium, barium, or lead salts by adding just the calculated quantity of sulfuric acid, filtering off the insoluble inorganic sulfate and concentrating the solution. They are solids usually crystallizing with water of crystallization and frequently are hygroscopic. They are very soluble in water and to a slight extent in some organic solvents. The sulfonic acids are as strong as the mineral acids. Benzene sulfonic acids and toluene sulfonic acids are sometimes employed as catalysts in reactions where a strong, non-volatile acid is required, as in the dehydration of alcohols to form olefins (p. 139).

**Reactions of Sulfonic Acids and Sulfonates.** The sulfonic acid group may be replaced by the hydroxyl group, the nitrile group, or hydrogen. All these reactions are of importance in the preparation of aromatic compounds. They are illustrated by the following equations:

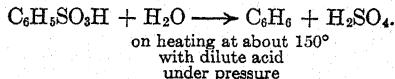
(a) *Replacement by OH:*



(b) *Replacement by C≡N:*



(c) *Replacement by H:*

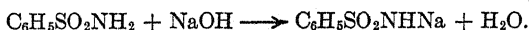


The acid chlorides of the aryl sulfonic acids are formed by the action of the chlorides of phosphorus on the free acids or the sodium salts.



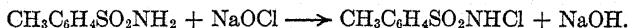
**Aryl Sulfonamides.** The action of ammonia on the aryl sulfonyl chlorides yields the unsubstituted aryl sulfonamides. These are crystalline solids; benzene and toluene sulfonamides are somewhat soluble in organic solvents and in water. The para toluene sulfonamide,  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2$ , is a by-product of the manufacture of saccharin (p. 428). The sulfonamides which

contain a replaceable hydrogen atom dissolve in aqueous sodium hydroxide forming salts.

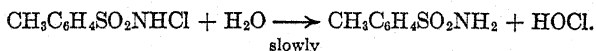


On acidifying, the sulfonamide is precipitated. The aryl sulfonyl group (*e.g.*,  $\text{C}_6\text{H}_5\text{SO}_2-$ ), is very acidic in its influence. The corresponding OH compounds (the sulfonic acids) are strong acids and the  $-\text{NHR}$  derivatives are strong enough acids to dissolve in aqueous sodium hydroxide. (It will be recalled that the amides of the organic acids were not acidic enough to manifest this property in aqueous solution, p. 151.)

The chlorosulfonamides are interesting compounds prepared by the action of sodium hypochlorite on the sulfonamides.

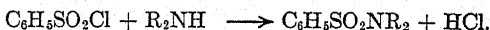
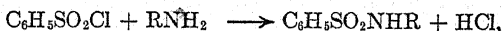
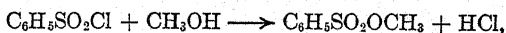


They are crystalline solids which in water solution slowly liberate hypochlorous acid.



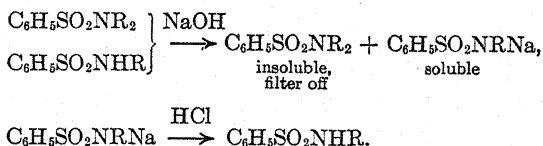
For this reason they have been used as an effective antiseptic agent for wounds. Chloramine T is a sodium salt,  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NClNa}$ , and is soluble in water: dichloramine T is  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NCl}_2$ , and is soluble in organic solvents.

**Benzene Sulfonyl Chloride as Reagent for Amines.** Like other acid chlorides, the chlorides of the aryl sulfonic acids will react with water, alcohols, or amines. The reactions with benzene sulfonyl chloride are:

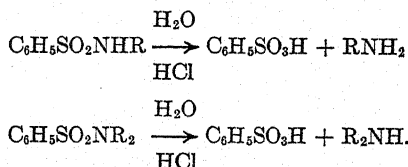


The last two reactions are of importance as being the basis of the Hinsberg method of separating and characterizing amines. Obviously tertiary amines ( $\text{R}_3\text{N}$ ) can not react with the acid chloride. They may be separated by extraction or distillation after the primary and secondary amines have been converted into the substituted benzene sulfonamides,  $\text{C}_6\text{H}_5\text{SO}_2\text{NHR}$  and  $\text{C}_6\text{H}_5\text{SO}_2\text{NR}_2$ . These two sulfonamides are readily separated by

treating with an excess of sodium hydroxide. The sulfonamide obtained from the primary amine has a hydrogen atom on the nitrogen; this hydrogen is sufficiently acidic, due to the influence of the sulfonyl group, to cause the compound to dissolve in sodium hydroxide. The other substance derived from the secondary amine contains no replaceable hydrogen, can not form a salt, and does not dissolve.

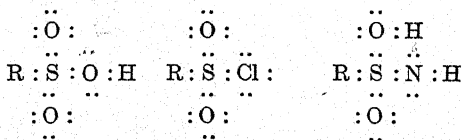


The sulfonamides on boiling with 25 per cent hydrochloric acid are hydrolyzed regenerating the amines and sulfonic acid. Thus, after the two sulfonamides have been separated, as described, the amines are recovered by hydrolysis.



**Structure of Sulfonyl Compounds.** In the sulfonic acids, the sulfur atom is directly joined to carbon. The contrast between the sulfonic acids and the esters of sulfuric acid has been discussed in connection with the aliphatic sulfonic acids (p. 266).

As in the case of the sulfoxides or sulfones (p. 268) the linkage between oxygen and sulfur in the sulfonic acids and their derivatives is sometimes indicated by a double bond. We have seen, however, that a consideration of the electronic valence formulas of these sulfur compounds shows that this method of formulation is misleading. The electronic structures of a sulfonic acid, a sulfonyl chloride, and a sulfonamide are shown below:



(The electronic structure of the aryl group R is not written except for the one link joining the carbon atom to the sulfur.) It is probably not worth while to try to represent the special sulfur to oxygen linkage in these compounds every time the formula is written. With suitable mental reservations, such

noncommittal formulas as  $\text{C}_6\text{H}_5\text{SO}_2\text{OH}$ ,  $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ , and  $\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$  are convenient.

### PHENOLS

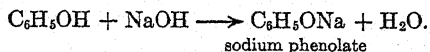
The hydroxy derivatives of aromatic hydrocarbons which have the OH group directly attached to the ring are called phenols. Phenol, or carbolic acid,  $\text{C}_6\text{H}_5\text{OH}$ , is the most important representative of the class. It is a colorless, crystalline substance which melts at  $41^\circ$ . Small amounts of water dissolved in phenol lower the melting point below room temperature.

The phenols which are derivatives of toluene are called cresols. The physical properties of these substances and phenol are listed below:

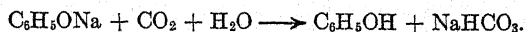
NAME	FORMULA	BOILING POINT	MELTING POINT	SOLUBILITY GRAMS IN 100 GRAMS OF $\text{H}_2\text{O}$
Phenol	$\text{C}_6\text{H}_5\text{OH}$	$182^\circ$	$41^\circ$	8 at $25^\circ$ miscible at $68^\circ$
<i>o</i> -Cresol	$\text{CH}_3\text{C}_6\text{H}_4\text{OH} (o)$	$191^\circ$	$31^\circ$	3 at $35^\circ$
<i>m</i> -Cresol	$\text{CH}_3\text{C}_6\text{H}_4\text{OH} (m)$	$203^\circ$	$10^\circ$	2.4 at $25^\circ$
<i>p</i> -Cresol	$\text{CH}_3\text{C}_6\text{H}_4\text{OH} (p)$	$201^\circ$	$35^\circ$	2.4 at $40^\circ$

As would be expected, the introduction of one OH group has made the substances somewhat soluble in water.

**Reactions of Phenols.** All the simple phenols (with the exception of the nitrophenols) are very weak acids but are sufficiently acidic to dissolve in sodium hydroxide.<sup>1</sup>



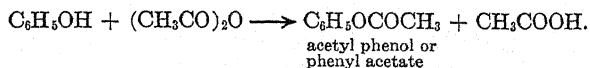
They will not, however, dissolve in sodium bicarbonate solution, thus differing in general from organic acids which contain the carboxyl group. Since they are weaker acids than carbonic acid, the following reaction takes place when carbon dioxide is passed through a water solution of their salts:



The hydroxyl group in phenols is very different from that in alcohols. The acyl derivatives (the esters) can not be made by

<sup>1</sup> The dissociation constant of phenol is about  $1.7 \times 10^{-10}$ . (Compare p. 84.)

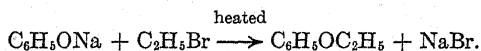
direct esterification. They are prepared by the use of acid anhydrides.



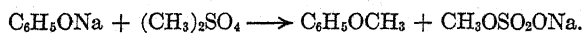
The aryl halides can not be readily prepared from phenols either by the action of the phosphorus trihalides or by the action of halogen acids. With phosphorus pentachloride or bromide, however, phenols yield the corresponding halides, but in poor yields.

In general, phenols are to be contrasted with alcohols and also with acids. They form a separate class by themselves and are most closely related to the enols (p. 232). If we compare the Kekulé formula for phenol with the formula for an enol the analogy is evident; both compounds contain the grouping  $-\text{C} = \text{C}(\text{OH})-$ . *The hydroxyl group directly attached to an unsaturated carbon linkage is acidic.*

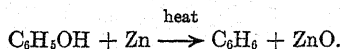
Phenol ethers are readily prepared by the action of an alkyl halide on the sodium salt of a phenol (sodium phenolate):



Dimethyl sulfate may be used in place of methyl iodide in the preparation of the methyl ethers.



Phenols can be converted into the parent hydrocarbon by heating to a high temperature with zinc dust:



When a solution of a phenol is treated with ferric chloride, an intense color is produced, which is blue, green, red, or violet depending on the other groups in the molecule.

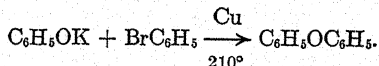
**Production of Phenol.** For many years phenol was obtained solely from coal tar. In the refining of this substance, it is found in the "middle oils," and it is obtained from them by extraction with aqueous sodium hydroxide. During the World War enormous quantities of phenol were needed to make the explosive trinitrophenol (picric acid), and to meet this demand synthetic phenol was produced. This synthetic method involves the preparation of sodium benzene sulfonate by the method previously

described (p. 348). This salt is then fused with sodium hydroxide, and sodium phenolate is formed. On dissolving the melt in water and acidifying phenol separates. It can then be purified by distillation. (The equations for the reactions involved in this process are given on pages 348 and 349.)

In more recent years the demand for an abundant and cheap supply of phenol became so great that a new method was worked out. In this process phenol is made from chlorobenzene. Chlorobenzene is heated with sodium hydroxide solution to a temperature of 350°–380° under very high pressures. This is done in a continuous tubular system of copper; some diphenyl ether,  $\text{C}_6\text{H}_5\text{OC}_6\text{H}_5$ , must be added. Under these conditions the chlorine atom is replaced by ONa.

**Industrial Uses of Phenol.** The increased demand for phenol is largely due to the growth of the synthetic resin industry. Synthetic resins are used in the manufacture of fountain pens, phonograph records, pipe stems, and as an insulator in electrical equipment. "Bakelite" is a synthetic resin formed by the action of formaldehyde on phenol in the presence of ammonia. This industry requires not only large amounts of phenol but also of formaldehyde (p. 128). Great quantities of phenol are also used in the manufacture of drugs, photographic developers, and dyes. Phenol itself is an excellent antiseptic, and dilute water solutions of it are widely used for this purpose (usually called carbolic acid). In 1924, 10,500,000 pounds of phenol were produced in the United States; in 1936, 49,000,000 pounds, of which about 90 per cent was prepared by synthetic methods. These figures indicate the industrial importance of the substance.

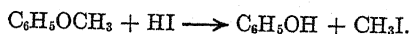
**Phenol Ethers.** The preparation of phenol ethers by the alkylation of phenols has been just discussed. Diphenyl ether,  $\text{C}_6\text{H}_5\text{OC}_6\text{H}_5$  (b.p. 259°), can be prepared by heating phenol with a dehydrating agent such as zinc chloride or by the action of bromobenzene on potassium phenolate. Finely divided metallic copper is an essential catalyst for this reaction:



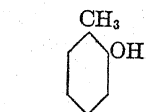
Diphenyl ether is a by-product of the industrial process for preparing phenol from chlorobenzene. The amount formed in this process seems to indicate a state of equilibrium. Unless this

by-product is desired, diphenyl ether is added to each charge, thus avoiding the further formation of this compound. Diphenyl ether finds use as a high temperature heat transfer medium.

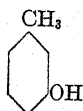
The most important phenyl ethers are **anisole**,  $\text{C}_6\text{H}_5\text{OCH}_3$ , a liquid which boils at  $154^\circ$ , and **phenetole**,  $\text{C}_6\text{H}_5\text{OC}_2\text{H}_5$ , which boils at  $172^\circ$ . They are neutral substances insoluble in water. When heated with aluminum chloride or boiled with hydrobromic or hydriodic acid, the phenol ethers are cleaved with the regeneration of the phenol:



**Hydroxyl Derivatives of Alkyl Benzenes.** The hydroxyl derivatives of toluene are the **cresols**. Their physical properties are given in the table on page 352.



ortho cresol  
or  
2-hydroxytoluene



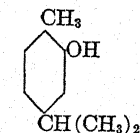
meta cresol  
or  
3-hydroxytoluene



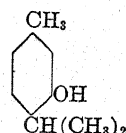
para cresol  
or  
4-hydroxytoluene

They are recovered from coal tar and used as antiseptics and, to some extent, in the preparation of other aromatic compounds.

**Thymol** and **carvacrol** are two hydroxyl derivatives of **para-cymene** (p. 339) which occur in many essential oils.



carvacrol

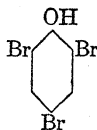


thymol

Thymol melts at  $51^\circ$  and boils at  $232^\circ$ ; carvacrol is a liquid at room temperature (m.p.  $+0.5$ ) and boils at  $237^\circ$ . Both compounds resemble phenol in their chemical reactions. Thymol is used in medicinal preparations as an antiseptic. It is much less poisonous than phenol.

**Halogenated Phenols.** The hydroxyl group in phenol orients ortho and para and also makes the replacement of the hydrogen atoms in those positions *easier* than in the parent hydrocarbon. Thus, if an aqueous solution of phenol is treated with bromine

water, a white precipitate is at once formed; this is an unstable compound, tribromophenolbromide,  $\text{Br}_4\text{C}_6\text{H}_2\text{O}$ . On treating with sodium bisulfite solution, the extra halogen atom is removed and tribromophenol is formed (m.p.  $96^\circ$ ). This compound has the bromine atoms in the ortho and para positions. It is named as 2, 4, 6-tribromophenol. This reaction is often used for the identification of phenol.



### QUESTIONS AND PROBLEMS

1. Write the structural formulas of the substances you would expect to obtain by the nitration of: (a) nitrobenzene; (b) toluene; (c)  $\text{C}_6\text{H}_5\text{COOH}$ ; (d)  $\text{C}_6\text{H}_5\text{Cl}$ . What products would be obtained by the bromination of these same compounds?

2. Write the electronic structure of the sodium salt of  $\text{C}_6\text{H}_5\text{SO}_2\text{NHR}$ .

Why is the structure  $\text{C}_6\text{H}_5-\overset{\text{O}}{\underset{\text{O}}{\text{S}}}=\text{NR}$  for the negative ion incorrect?

3. What two reactions of bromobenzene are similar to reactions of ethyl bromide? In what respects do these compounds differ?

4. Compare the chemical properties of: (a) phenol and methyl alcohol; (b)  $\text{C}_6\text{H}_5\text{ONa}$  and  $\text{C}_2\text{H}_5\text{ONa}$  (both are crystalline solids).

5. Given a solution of phenol and caproic acid ( $\text{C}_6\text{H}_{11}\text{COOH}$ ) in benzene, devise a method of separating the mixture into its three components without distillation. (Both phenol and caproic acid are only slightly soluble in water.)

6. What products (if any) would you expect if ortho cresol were treated with the following reagents: bromine water, a mixture of concentrated nitric and sulfuric acids, concentrated aqueous sodium hydroxide, glacial acetic acid and a very little sulfuric acid?

7. What products would you expect to obtain by the nitration of the following compounds: ortho xylene, ortho dibromobenzene, para chloronitrobenzene?

8. Write equations showing how you would separate a mixture of  $\text{CH}_3\text{NH}_2$ ,  $(\text{CH}_3)_2\text{NH}$ ,  $(\text{CH}_3)_3\text{N}$  and  $(\text{CH}_3)_4\text{NOH}$ .

9. Outline the steps in the preparation of chloramine T from coal tar. What products would you expect to obtain if an alkaline solution of this compound were warmed with acetone?

10. By what reactions would you decide whether a substance was  $\text{CH}_3\text{C}_2\text{H}_4\text{OCH}_3$  (1, 4),  $\text{C}_2\text{H}_5\text{C}_6\text{H}_4\text{OH}$  (1, 4), or  $\text{C}_6\text{H}_5\text{OC}_2\text{H}_5$ ? Write equa-

tions showing how you would synthesize all three substances from coal tar and aliphatic compounds.

11. State with reactions how you would differentiate between  $\text{C}_6\text{H}_5\text{OH}$  and  $\text{CH}_3(\text{CH}_2)_3\text{COOH}$ ;  $(\text{C}_6\text{H}_5)_2\text{O}$  and  $\text{C}_6\text{H}_5\text{OCH}_3$ ;  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$  and  $\text{CH}_3\text{C}_6\text{H}_4\text{Cl}$ -1, 4.

12. A substance A having the empirical formula  $\text{C}_6\text{H}_3\text{OCl}_3$  was found to be soluble in dilute alkali. When distilled with zinc dust it lost its oxygen and when treated with 1 mole of bromine only one product was formed,  $\text{C}_6\text{H}_2\text{Cl}_3\text{Br}$ . What is the structure of A?

## CHAPTER XX

### AROMATIC NITRO COMPOUNDS, AMINES, AND DIAZONIUM SALTS

**The Nitration of Aromatic Compounds.** The hydrogen atoms which are attached to the aromatic ring are readily replaced by the nitro group. This is one of the characteristic reactions of aromatic compounds. The nitration is usually carried out by treating the substance with a mixture of concentrated nitric and sulfuric acids. The sulfuric acid itself does not react, but by combining with the water present the nitric acid is made a more powerful nitrating agent. Some compounds like phenol are nitrated even by dilute nitric acid.

The **nitro compounds** are quite distinct from the esters of nitrous acid. A comparison of the structural formulas of **nitrobenzene** (formed by the nitration of benzene),  $C_6H_5 - NO_2$ , and ethyl nitrite,  $C_2H_5 - O - N = O$ , makes this evident. In the nitro compounds there is a carbon to nitrogen linkage. Unlike esters, *nitro compounds are not hydrolyzed.*

**Importance of Nitro Compounds.** Aromatic nitro compounds are of importance because of their use as explosives, and because they may be readily reduced to the corresponding **primary amines**. These in turn are the starting points in the manufacture of many dyes. The presence of one or more nitro groups in an aromatic nucleus markedly influences the chemical properties of other atoms or groups in the molecule; this is particularly true if the groups are in the ortho and para positions. The nitro group is almost unique in the extent of this influence which it exerts. For this reason we shall often have occasion to refer to the peculiar properties of nitro phenols, nitro amines, and nitro halogen compounds.

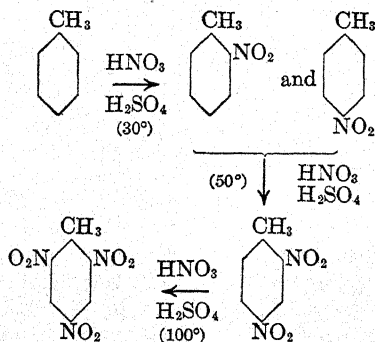
**The Products of the Nitration of Benzene and Toluene.** The chief products which may be obtained by the nitration of benzene and toluene are listed on the following page; they are all insoluble in water.

NAME	FORMULA	BOILING POINT	MELTING POINT
Nitrobenzene	$C_6H_5NO_2$	211°	+ 6°
<i>m</i> -Dinitrobenzene	$C_6H_4(NO_2)_2(m)$	302°	90°
<i>o</i> -Nitrotoluene	$CH_3C_6H_4NO_2(o)$	222°	- 11°
<i>p</i> -Nitrotoluene	$CH_3C_6H_4NO_2(p)$	238°	51°
<i>m</i> -Nitrotoluene (obtained in small amounts in the mononitration)	$CH_3C_6H_4NO_2(m)$	231°	16°
2, 4-Dinitrotoluene	$CH_3C_6H_3(NO_2)_2$	300°	70°
2, 4, 6-Trinitrotoluene (T.N.T.)	$CH_3C_6H_2(NO_2)_3$	—	81°

**Nitrobenzene** is a slightly yellow liquid with a characteristic odor somewhat reminiscent of almonds. It is prepared on a very large scale chiefly for use in the preparation of aniline. The nitration of benzene is accomplished by agitating a mixture of the hydrocarbon with sulfuric and nitric acids. The product is insoluble in the nitrating mixture and may be readily separated. It is purified by washing with water and then distilling.

The introduction of a second nitro group into benzene is more difficult than the introduction of the first. This fact illustrates the general rule that the presence of a meta-orienting group makes substitution more difficult than in benzene itself. In order to prepare **meta dinitrobenzene**, a higher temperature is required and fuming nitric acid is employed. The introduction of a third nitro group into benzene is very difficult.

Toluene may be nitrated in a step-wise manner to 2, 4, 6-trinitrotoluene:



Since toluene contains the methyl group which orients ortho

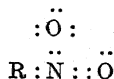
and para, its nitration is more readily accomplished than that of benzene itself. This contrast is particularly evident in the formation of the 2, 4, 6-trinitrotoluene without difficulty. The nitration is carried out in three steps, each at a somewhat higher temperature.

**Aromatic Nitro Compounds as High Explosives.** Trinitrotoluene, usually called T.N.T., was prepared in enormous quantities during the World War and was used in shells as a high explosive. It is relatively insensitive to shock and can, therefore, be used in filling projectiles which are fired from guns and which could not contain the more sensitive nitrates of cellulose (p. 318). It is detonated by means of a special charge called a booster, which is ignited by a time fuse or on impact. The explosion of aromatic nitro compounds, like that of glycerine trinitrate, is a rapid combustion in which the oxygen comes from *within* the molecule itself. Because the nitro groups supply this oxygen, the explosive force increases with the number of nitro groups. Although trinitrobenzene is an excellent explosive, it is so difficult to introduce the third nitro group into benzene that the manufacture is out of the question. A war explosive is made from benzene by first preparing phenol (p. 353), which is then nitrated to picric acid (P.A.). This differs from T.N.T. only in having an OH group in place of a methyl.

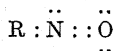
**Structure of Nitro Compounds.** The fact that nitro compounds contain a nitrogen to carbon linkage is established by their reduction to primary amines ( $\text{RNH}_2$ ). The isomeric nitrites do not yield any reduction product in which a nitrogen atom is thus attached. The fact that nitro compounds are not hydrolyzed has already been emphasized. The carbon to nitrogen linkage in both the aliphatic and aromatic nitro compounds is firm. The *only exception* to this statement is the behavior of polynitro compounds which contain *two nitro groups* in the *ortho* or *para position*. In such compounds *one nitro group may be replaced* by  $-\text{OH}$ ,  $-\text{NH}_2$ , or  $-\text{OCH}_3$  by the vigorous action of sodium hydroxide, ammonia, or sodium methylate, respectively. These reactions are indicative of the peculiar effect of a nitro group on another atom or group in the *ortho* and *para position*, and are not to be regarded as typical of the usual aromatic nitro compounds.

It was at one time usual to write the nitro group as  $-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \end{array}$ , but a consideration of the electronic formula shows that this formulation is misleading. The electronic equivalent of this structure would involve ten electrons in the outer shell of the nitrogen atom. This is extremely unlikely as we have emphasized before; the problem is exactly the same as the one which arose in connection with the amine oxides (p. 167), sulfones (p. 268), and sulfonyl

compounds (p. 351). The correct electronic formula for a nitro compound  $\text{RNO}_2$  is as follows:



This may be written as  $\text{R}-\overset{\text{O}}{\underset{\parallel}{\text{N}}^+}-\text{O}^-$ . There is no real distinction, of course, between the two oxygen atoms, and the nitro group, like the carboxyl ion exhibits resonance (p. 260). For most purposes the noncommittal formula,  $\text{RNO}_2$ , is most useful. The electronic structure of the nitroso compound (p. 367) ( $\text{R}-\text{N}=\text{O}$ ) corresponds to an orthodox double linkage:



the relation between a nitroso compound and a nitro compound is very similar to that between an amine and an amine oxide (p. 167). It is interesting that in both cases one oxygen atom can be removed by reducing agents, amine oxides yielding amines and nitro compounds, nitroso compounds.

### NITROPHENOLS

**Nitration of Phenol.** The ortho and para nitrophenols may be prepared by the nitration of phenol with dilute nitric acid. The fact that dilute acid may be employed is another illustration of the accelerating influence of a group of Class I (p. 345) on substitution reactions. The isomers are separated by steam distillation. The **ortho nitrophenol** is volatile with steam and intensely yellow; it melts at  $45^\circ$ . The **para nitrophenol** melts at  $114^\circ$ . Further nitration of these isomers yields **2, 4-dinitrophenol**,  $\text{C}_6\text{H}_3(\text{OH})(\text{NO}_2)_2$  (m.p.  $112^\circ$ ); and eventually **2, 4, 6-trinitrophenol**,  $\text{C}_6\text{H}_2(\text{OH})(\text{NO}_2)_3$  (m.p.  $123^\circ$ ), **picric acid** (P.A.), an important high explosive. The nitrophenols are only slightly soluble in water.

**Picric Acid.** In the industrial preparation of picric acid, phenol is dissolved in concentrated sulfuric acid and then treated with nitric acid, first at  $0^\circ$  and then  $100^\circ$ . The process probably involves first the formation of para phenol sulfonic acid,  $\text{C}_6\text{H}_4(\text{OH})\text{SO}_3\text{H}$ , and then the replacement by the nitro group of both the sulfonic acid group and the ortho hydrogen atom, yielding 2, 4-dinitrophenol. The final nitration at  $100^\circ$  introduces the third nitro group.

The solutions of picric acid are intensely yellow, and wool and silk may be dyed by immersion. The metallic salts of picric acid (the picrates) are sensitive explosives when dry and easily detonate when subjected to mechanical

shock. Picric acid itself, however, like T.N.T., is not sensitive and can be used in filling shells. Picric acid is often used in the laboratory in the isolation of bases since its salts with organic bases are often but slightly soluble and usually nicely crystalline. Picric acid forms loose molecular addition compounds with many aromatic hydrocarbons, particularly those containing a number of rings. These crystalline **molecular compounds** are sometimes useful in separating the complex aromatic hydrocarbons.

**The Acidic Properties of the Nitrophenols.** The peculiar influence of the nitro group is strikingly shown by a comparison of the acidic properties of phenol and its nitro derivatives.

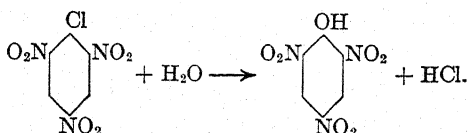
Phenol and most of its simple derivatives are such weak acids that they will not dissolve in sodium bicarbonate. 2, 4-Dinitrophenol, however, will dissolve in an aqueous solution of this reagent because it is as strong an acid as formic acid and readily replaces carbonic acid from its salts. Trinitrophenol (picric acid) is nearly as strong as the mineral acids. The dissociation constants are as follows:

Phenol	$1.7 \times 10^{-10}$
<i>p</i> -Nitrophenol	$6.4 \times 10^{-8}$
2, 4-Dinitrophenol	$1.0 \times 10^{-4}$
Picric acid	$1.6 \times 10^{-1}$

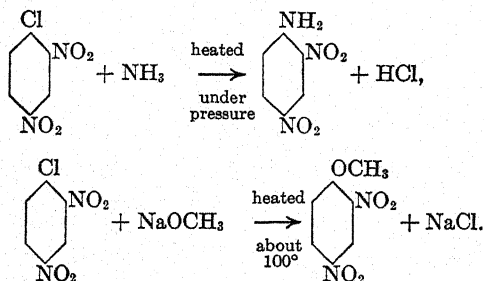
The dissociation constants of carbonic acid are:  $\text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+$ ,  $1 \times 10^{-7}$  and  $\text{HCO}_3^- \rightleftharpoons \text{CO}_3^{2-} + \text{H}^+$ ,  $5 \times 10^{-11}$  (p. 84). Many phenols may be separated from acids and nitrophenols by the difference in solubility in sodium bicarbonate solution. The solubility of an acid in a given alkaline solution (with the formation of a salt) depends on two factors: (1) the strength of the acid group, and (2) the solubility. Phenols of high molecular weight are often only very slightly soluble and will not dissolve even in dilute sodium hydroxide. Similar considerations apply to acids. However, as a general rule, acids of low molecular weight may be extracted from an ether solution by sodium bicarbonate or sodium carbonate while phenols require sodium hydroxide. The nitrophenols, however, are often extracted by sodium carbonate since they are stronger acids if the nitro groups are in the ortho or para position to the hydroxyl. Like the phenols, many highly enolic substances are soluble in dilute sodium hydroxide and may be extracted by this reagent.

**Reactivity of Nitro Aryl Halides.** We have just seen the marked effect of a nitro group in the ortho or para position on the acidity of a phenol. The nitro group modifies the molecule so that the hydroxyl group is more acidic. The influence of the nitro group is not confined to a hydroxyl group, but also extends to a halogen atom in the ortho or para position. In this case, the effect of the

nitro group is to make the halogen atom much more readily replaced by such groups as OH, NH<sub>2</sub>, and OCH<sub>3</sub>. The simple aryl halides (*e.g.*, C<sub>6</sub>H<sub>5</sub>Cl), like the vinyl halides, are extremely unreactive. The introduction of a nitro group in the ortho or para position, however, makes the halogen atom of an aryl halide sufficiently reactive so that it may be readily replaced by many groups. The effect is cumulative and the chlorine atom in 2, 4, 6-trinitrochlorobenzene (picryl chloride) is replaced by hydroxyl when the compound is boiled merely with water:

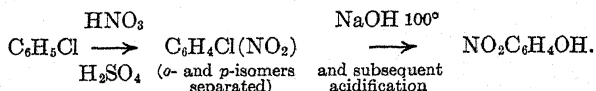


In the case of the mononitro compounds (ortho and para nitrochlorobenzene) heating above 100° with *sodium hydroxide* is necessary to bring about a similar reaction. The nitro aryl halides (with the nitro groups ortho or para to the halogen atom) will also react with ammonia or sodium methylate, yielding an amine or a phenolic ether. As an illustration, the behavior of 2, 4-dinitrochlorobenzene may be cited:



**Nitrophenols from Chlorobenzene.** The enhanced reactivity of the halogen atom in certain of the nitro aryl halides is taken advantage of in the preparation of the nitrophenols. The direct nitration of phenol with the formation of the ortho and para derivatives is troublesome, because phenol is easily oxidized by nitric acid. This difficulty may be avoided by starting with chlorobenzene and proceeding to the nitrophenols through the nitro-

chlorobenzenes. The steps in the entire synthesis are as follows:



### AROMATIC AMINES

**Classification.** The aromatic amines, like the aliphatic amines, are divided into three classes: (1) **primary amines**, (2) **secondary amines**, and (3) **tertiary amines**. As an example of each class we may mention: (1) **aniline**,  $\text{C}_6\text{H}_5\text{NH}_2$ , (2) **diphenyl amine**,  $(\text{C}_6\text{H}_5)_2\text{NH}$ , and (3) **triphenyl amine**,  $(\text{C}_6\text{H}_5)_3\text{N}$ . Mixed aliphatic-aromatic amines are also known; for example, **monomethylaniline**,  $\text{C}_6\text{H}_5\text{NHCH}_3$ , and **dimethylaniline**,  $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$ . The primary aromatic amines and the mixed amines are usually weak bases which form salts with mineral acids; the secondary and tertiary aromatic amines are too weak to form salts which are stable in water solution.

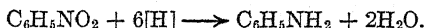
The primary amines are by far the most important since they may be readily prepared by reducing aromatic nitro compounds and can be converted into many useful products, particularly dyestuffs. Indeed, the name of the commonest primary amine, — aniline, — has become so associated with the synthetic dye industry that the term “aniline dyes” is often used synonymously with “coal tar dyes,” and covers many compounds which have no connection whatsoever with aniline.

**Physical Properties.** The physical properties of some common aromatic amines are given below:

NAME	FORMULA	BOILING POINT	MELTING POINT	SOLUBILITY GRAMS PER 100 GRAMS OF WATER
Aniline	$\text{C}_6\text{H}_5\text{NH}_2$	184°	— 6°	3.5 at 25°
<i>o</i> -Toluidine	$\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$	201°	— 21°	1.5 at 25°
<i>m</i> -Toluidine	$\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$	203°	— 32°	slightly soluble
<i>p</i> -Toluidine	$\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$	201°	+ 44°	0.730 at 21°
Monomethylaniline	$\text{C}_6\text{H}_5\text{NHCH}_3$	196°	— 57°	very slightly soluble
Dimethylaniline	$\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$	194°	+ 2°	very slightly soluble
Diphenyl amine	$(\text{C}_6\text{H}_5)_2\text{NH}$	302°	53°	insoluble
Triphenyl amine	$(\text{C}_6\text{H}_5)_3\text{N}$	365°	127°	insoluble

All the substances listed in the table except the last two are soluble in dilute hydrochloric or sulfuric acid because they form water-soluble salts with these acids.

**Preparation of Aniline, a Primary Amine.** Aniline,  $C_6H_5NH_2$ , is prepared by the reduction of nitrobenzene:



In the laboratory, tin and hydrochloric acid are usually employed; industrially, the cheaper scrap iron replaces the tin and only a little acid is employed. The industrial process, thus, is essentially the reduction of nitrobenzene by iron and water, the products

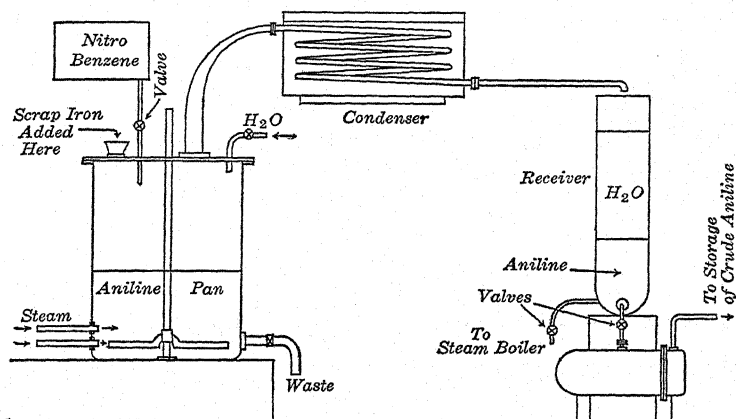
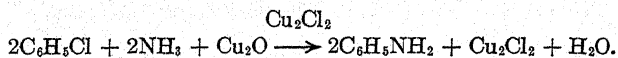


Fig. 27. Diagram illustrating the essential equipment used in the industrial preparation of aniline.

The nitrobenzene, water and a little acid are first introduced into the reaction vessel. Scrap iron is dropped in through a man-hole and the mixture stirred. After the reduction is complete, steam is introduced; the vapors are condensed and the distillate allowed to settle in tall tanks. The crude aniline is drawn off; the water goes to the steam generator.

being aniline and ferric hydroxide; these are separated by steam distillation (Fig. 27). Nitro compounds are smoothly reduced to amines by catalytic hydrogenation.

Aniline is also made commercially by heating chlorobenzene and ammonia at about  $200^\circ$  with a mixture of cuprous oxide and cuprous chloride. The latter is a catalyst while the cuprous oxide participates in the reaction:



The recovered cuprous chloride is treated with alkali to convert most of it to the oxide, and the mixture is then used for the next charge.

The toluidines,  $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$ , are prepared by the nitration of toluene and the reduction of the products. Like aniline they are important dye intermediates. The ortho and para compounds are most readily obtained since the nitration of toluene yields chiefly the *o*- and *p*-nitrotoluenes.

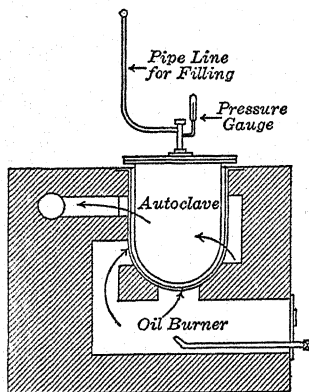
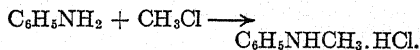


Fig. 28. Autoclave employed in the industrial preparation of dimethylaniline.

**Monomethylaniline and Dimethylaniline.** These amines are formed when aniline is heated with methyl alcohol and hydrochloric acid under pressure. The apparatus in which such reactions are carried out under pressure is called an autoclave (Fig. 28). The methyl alcohol and hydrogen chloride first form methyl chloride which then reacts with the primary amine (p. 159), yielding the hydrochloride of monomethylaniline:



By varying the temperature and proportions of reacting materials either monomethylaniline or dimethylaniline may be prepared. Both are important substances in the manufacture of dyes.

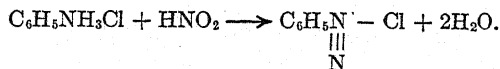
**Aromatic Amines Are Weak Bases.** The weak basic strength of aniline and its two derivatives is shown by the following basic dissociation constants:

Aniline,	$K_B = 3.5 \times 10^{-10}$
Methylaniline,	$K_B = 2.6 \times 10^{-10}$
Dimethylaniline,	$K_B = 2.4 \times 10^{-10}$

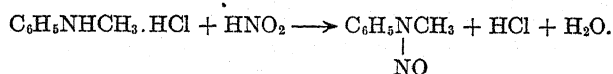
It will be recalled that ammonia has the value  $2 \times 10^{-5}$  and the aliphatic amines about  $5 \times 10^{-4}$  (p. 158).

**Reaction with Nitrous Acid.** Primary, secondary, and tertiary amines differ in their reaction with nitrous acid. This may be illustrated by comparing the action of this reagent with aniline, monomethylaniline, and dimethylaniline. With the first, a water-

soluble **diazonium salt**,  $C_6H_5N_2Cl$ , is formed. This compound will be further considered shortly.

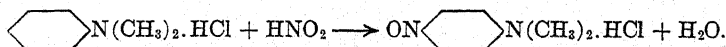


With monomethylaniline, a yellow, oily **nitroso compound** is produced:

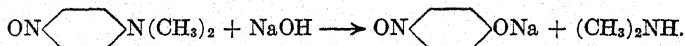


This substance is so weak a base that it will not dissolve in aqueous acid solutions. When treated with alcoholic hydrogen chloride, the nitroso group migrates from the nitrogen to the para position of the nucleus.

The para hydrogen atom in the nucleus of dimethylaniline is unusually reactive and is replaced by the **nitroso group** when the compound is treated with dilute nitrous acid. The product is the hydrochloride of *p*-nitroso-dimethylaniline which is a yellow, crystalline solid.

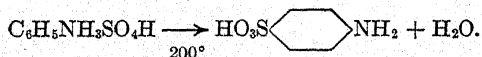


The nitroso group, like the nitro group, profoundly effects an atom or group attached to the ortho or para position of the aromatic nucleus. For this reason, para nitrosodimethylaniline, on boiling with alkali, decomposes forming dimethyl amine and the salt of the corresponding hydroxyl compound (nitroso phenol):



This is probably the best method of preparing pure dimethyl amine.

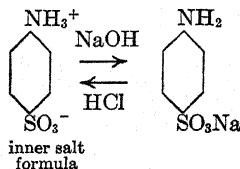
**Sulfanilic Acid.** Aniline may be sulfonated, producing the para sulfonic acid. The amine is first neutralized with concentrated sulfuric acid, forming the solid **aniline acid sulfate**,  $C_6H_5NH_3SO_4H$ . This, on baking in an oven at  $200^\circ$ , forms sulfanilic acid and water:



Sulfanilic acid is a solid only slightly soluble in organic solvents and in water. It is non-volatile and has no definite melting point;

in these respects it resembles an inorganic salt rather than an organic compound. It is soluble in sodium carbonate or sodium hydroxide, forming a sodium salt; acidification precipitates sulfanilic acid again. It has such weak basic properties that it does not dissolve even in concentrated hydrochloric acid.

**Inner Salt Formula for Sulfanilic Acid.** All the facts mentioned in the last paragraph are best represented by the so-called inner salt formula written below:

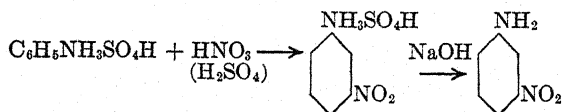


This formula is written to indicate that an internal neutralization has occurred. In this process the acid hydrogen of the sulfonic acid group has added to the  $\text{NH}_2$  group. The "linkage" between the  $\text{NH}_3^+$  group and the  $\text{SO}_3^-$  group is of the sort which we meet in inorganic salts such as sodium chloride and ammonium sulfate. This linkage we are quite certain is not a linkage in the sense of the ordinary valence formulas used in organic chemistry; it merely represents an electrical field between two charged atoms or molecules (see p. 163).

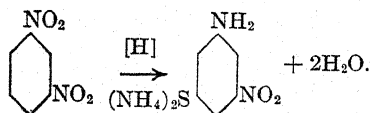
In the case of the inner salts, we imagine that the positive and negative charges are localized on particular groups of the large molecule. The simple formula,  $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_3\text{H}$ , is often written for sulfanilic acid, but the representation,  $\text{NH}_3^+\text{C}_6\text{H}_4\text{SO}_3^-$ , is to be preferred. Inner salts differ from salts such as sodium chloride in that the positive and negative ions are not free to part company in solution. Inner salts are ionized but not dissociated.

**Nitration of Aniline.** When aniline is nitrated in the usual way with a mixture of nitric and sulfuric acids there is a great deal of oxidation, but at a low temperature it is possible to obtain considerable amounts of the nitration product, which is **meta nitroaniline**,  $\text{C}_6\text{H}_4\text{NH}_2(\text{NO}_2)$ . At first sight this might appear to be contrary to the rules of orientation. The explanation for the apparent anomaly is that aniline sulfate is the substance which is really nitrated in the acid mixture, and that the  $-\text{NH}_3^+$  group

directs the incoming group into the meta position:

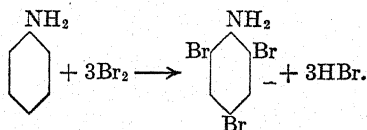


Meta nitroaniline is also prepared from meta dinitrobenzene which in turn can be readily prepared by the nitration of benzene. The reduction of one nitro group only is accomplished by heating the dinitro compound with ammonium sulfide. This rather unusual reagent is only effective in reducing groups which are very easily reduced. In the case at hand its action is confined to one nitro group:



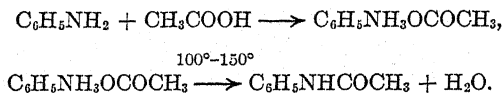
The **ortho** and **para nitroanilines** (nitranilines) are prepared industrially by an indirect method described on page 370.

**Tribromoaniline.** Although the nitration of aniline appears abnormal, aniline is very similar to phenol in most substitution reactions. For example, on treating aniline with dilute bromine water a white precipitate of 2, 4, 6-tribromoaniline,  $\text{Br}_3\text{C}_6\text{H}_2\text{NH}_2$ , is at once formed.

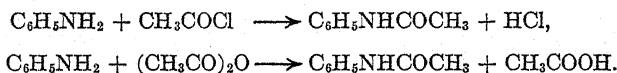


**Acetanilide**,  $\text{C}_6\text{H}_5\text{NHCOCH}_3$ , is the acetyl derivative of aniline. It is a substance of considerable importance both as an intermediate in the preparation of organic compounds and as a drug. It is one of the oldest of the so-called coal tar medicinals. It has an effect on the human system which causes the lowering of the temperature of a patient suffering with fever. A substance which has this action is said to be an **antipyretic** or **febrifuge**. Acetanilide has been used less extensively in recent years for this purpose because more efficient and relatively less harmful drugs have been synthesized (*e.g.*, phenacetin, p. 394).

The usual method of preparing acetanilide is exactly analogous to the preparation of acetamide from ammonium acetate:

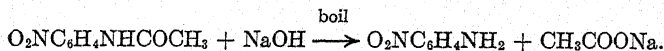


It may also be prepared by the action of acetyl chloride or acetic anhydride on aniline:



Acetanilide is a white crystalline solid which melts at  $114^\circ$ . It has no basic properties. In general, the acyl derivatives of the aromatic amines are crystalline solids which are easily purified. For this reason aromatic amines are often converted into their acyl compounds for purposes of identification. Organic acids may be identified by converting them into crystalline anilides by the reactions given above.

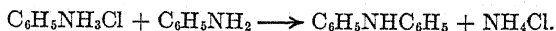
**Synthesis of Para Nitroaniline.** Acetanilide when nitrated with a mixture of sulfuric and nitric acids gives a mixture of the ortho and para nitro compounds; under special conditions the para isomer is the chief product. This affords a very convenient method of preparing para nitroaniline (para nitraniline), which, as we have seen above, is not the product of the direct nitration of aniline under the usual conditions. **Para nitroacetanilide** on boiling with sodium hydroxide is hydrolyzed, forming *p*-nitroaniline and sodium acetate. The reaction is analogous to the hydrolysis of amides and is a general one for all acyl derivatives of amines:



In the industrial preparation of para nitroaniline, the sodium acetate is converted into acetic acid which is used for preparing more acetanilide from aniline. Thus, the whole process may be considered as an *indirect nitration of aniline*; in order to get the proper orientation, a group is temporarily tied to the molecule and after it has served its purpose is removed. In this case the acetyl group also protects the molecule from the oxidation which occurs when aniline itself is nitrated.

**Nitroanilines as Dye Intermediates.** The nitroanilines are widely used in the dye industry; they are all solids insoluble in water but soluble in dilute mineral acids because of their weak basic properties. Their melting points are: ortho 72°, meta 112°, para 148°.

**Neutral Aromatic Amines.** Diphenyl amine,  $(C_6H_5)_2NH$ , and triphenyl amine,  $(C_6H_5)_3N$ , are representatives of the aryl secondary and tertiary amines. Diphenyl amine is prepared by heating an equimolecular mixture of aniline and aniline hydrochloride in an autoclave at 200°–230°:



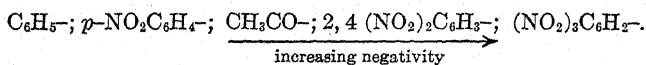
It is used in the manufacture of certain dyes and is frequently incorporated into nitrocellulose products in which it prevents spontaneous decomposition. The triphenyl amine is prepared by heating a mixture of diphenyl amine, iodobenzene, potassium carbonate, and copper powder. The catalytic effect of the copper is similar to its action in promoting the formation of diaryl ethers (p. 354).

The most interesting fact about the di- and tri-aryl amines is the almost entire absence of basic properties. Thus, diphenyl amine is so weak a base that it will dissolve in only the most concentrated acids. Triphenyl amine has no basic properties. We have pointed out earlier that the introduction of an acyl group into ammonia produced a neutral substance — an amide ( $RCONH_2$ ). We now see that two phenyl groups produce the same effect. If we were to examine the compound produced by the action of nitrous acid on monomethylaniline,  $C_6H_5N(NO)CH_3$  (p. 367), we should find that this also was devoid of basic properties. The replacement of the hydrogen atom on the basic group by  $-NO$  destroys the basic properties of monomethylaniline. We thus recognize that certain groups, such as the acyl group, the phenyl group, and the nitroso group, markedly affect the basicity of the nitrogen atom when they are attached to it. The alkyl group, however, is essentially like hydrogen since the alkyl amines are bases of about the same strength as ammonia.

**Basicity of the Nitroanilines.** In this connection, the behavior of the nitro derivatives of aniline is of interest. The introduction of a nitro group in the ortho or para position renders the compound less basic than aniline itself. The effect is particularly striking

in the case of 2, 4, 6-trinitroaniline,  $(\text{NO}_2)_3\text{C}_6\text{H}_2\text{NH}_2$ , which has no basic properties at all. This compound is related to picric acid as acetamide is to acetic acid and is often called **picramide**. Like other amides, but unlike aryl amines, it can be hydrolyzed by boiling with sodium hydroxide; sodium picrate is the product. It should be carefully noted that the nitration of phenol makes it a *stronger acid*; the nitration of aniline makes it a *weaker base*.

**Negative Groups.** A list of those groups which make ammonia less basic is useful in making approximate predictions as to the basic strength of organic amines. These groups are sometimes called *negative groups* and they are arranged below in what might be called an order of increasing negativity, the last group being the most effective:



The other acyl groups such as propionyl and butyryl would be placed with the acetyl group. It will be noted that all these groups are unsaturated groups, and the unsaturation is at the point of attachment of the group. It must be borne in mind that all these groups exert their influence only if *directly* linked to the nitrogen atom. The peculiar *indirect influence* of the nitro group in aromatic compounds, which is transmitted through the ring, should not be confused with the direct effect of negative groups.

The following table gives the basic dissociation constants of the  $-\text{NH}_2$  compounds which correspond to the negative groups listed above. The right-hand side of the table lists the corresponding  $-\text{OH}$  compounds and their acid dissociation constants.

GROUP	AMMONIA DERIVATIVE	$K_B$	WATER DERIVATIVE	$K_A$
$\text{C}_6\text{H}_5^-$	$\text{C}_6\text{H}_5\text{NH}_2$	$3.5 \times 10^{-10}$	$\text{C}_6\text{H}_5\text{OH}$	$1.7 \times 10^{-10}$
$p\text{-NO}_2\text{C}_6\text{H}_4^-$	$p\text{-NO}_2\text{C}_6\text{H}_4\text{NH}_2$	$1.0 \times 10^{-12}$	$p\text{-NO}_2\text{C}_6\text{H}_4\text{OH}$	$6.4 \times 10^{-8}$
$\text{CH}_3\text{CO}-$	$\text{CH}_3\text{CONH}_2$	*	$\text{CH}_3\text{COOH}$	$1.8 \times 10^{-5}$
$2, 4 (\text{NO}_2)_2\text{C}_6\text{H}_3^-$	$(\text{NO}_2)_2\text{C}_6\text{H}_3\text{NH}_2$	*	$(\text{NO}_2)_2\text{C}_6\text{H}_3\text{OH}$	$1.0 \times 10^{-4}$
$(\text{NO}_2)_3\text{C}_6\text{H}_2^-$	$(\text{NO}_2)_3\text{C}_6\text{H}_2\text{NH}_2$	*	$(\text{NO}_2)_3\text{C}_6\text{H}_2\text{OH}$	$1.6 \times 10^{-1}$

\* Too weak to form salts in water solutions. The  $K_B$  of  $\text{CH}_3\text{CONH}_2$  has been estimated as  $1 \times 10^{-16}$ ; that of  $(\text{NO}_2)_2\text{C}_6\text{H}_3\text{NH}_2$  as less than  $10^{-16}$ .

It will be recalled that water is a very weak acid ( $K_A = 1 \times 10^{-14}$ ) and ammonia a moderately strong base ( $K_B = 2 \times 10^{-5}$ ). Introducing the weakly negative phenyl group in place of one hydrogen atom of water makes a very weak acid, while introducing the strong negative group  $(NO_2)_3C_6H_2-$  produces a strong acid. The effect on the basicity of ammonia is just the reverse; the more negative the group the less basic is the  $-NH_2$  compound. A careful study of the table will show that the two effects of the negative groups are approximately the same numerically; thus, para nitroaniline is about 100 times ( $10^2$ ) as weak a base as aniline and para nitrophenol is about 100 times as strong an acid as phenol.

**Benzyl Amine.** The aryl amines are usually considered to include only those compounds in which one or more aryl groups are *directly* attached to the nitrogen atom. For this reason, benzyl amine,  $C_6H_5CH_2NH_2$ , is not classified as an aryl amine although it contains an aryl group. In fact, it has nothing in common with the aryl amines; its method of preparation and all its reactions are evidence of its close relationship to the aliphatic amines. For example, it may be prepared by the action of ammonia on benzyl chloride. On treating with nitrous acid it behaves like a typical aliphatic primary amine (p. 160) and not like aniline, — it does not form a diazonium salt but evolves nitrogen. Its basic strength ( $K_B = 2 \times 10^{-5}$ ) is not strikingly different from that of an aliphatic primary amine ( $CH_3NH_2$ ,  $K_B = 50 \times 10^{-5}$ ), which, it will be recalled, is much greater than that of the aryl amines (about  $10^{-10}$ ). A comparison of benzyl amine and the isomeric toluidines ( $CH_3C_6H_4NH_2$ ) is instructive, and, like the contrast between chlorotoluene and benzyl chloride (p. 434), illustrates that the characteristic peculiarities of aryl compounds are confined to those substances in which the functional group (or atom) is directly attached to the aromatic nucleus.

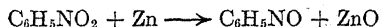
#### INTERMEDIATE REDUCTION PRODUCTS OF NITROBENZENE

The final reduction product of an aromatic nitro compound is a primary amine. Thus, as we have seen, the reduction of nitrobenzene with metals and acid yields aniline. By using less drastic reducing agents it is possible to isolate two substances intermediate between nitrobenzene and aniline; these are nitrosobenzene,  $C_6H_5NO$ , and phenylhydroxylamine,  $C_6H_5NHOH$ . (The name of the latter substance follows from its relation to hydroxylamine,  $NH_2OH$ .) If the reduction of nitrobenzene is carried out in an alkaline solution, these two compounds condense and the

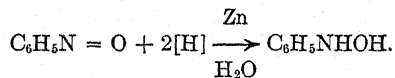
final products are either azoxybenzene,  $\text{C}_6\text{H}_5\text{N} = \text{NC}_6\text{H}_5$ , azo-

benzene,  $\text{C}_6\text{H}_5\text{N} = \text{NC}_6\text{H}_5$ , or hydrazobenzene,  $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$ . As there is some interesting chemistry connected with each one of these substances, they warrant a brief consideration.

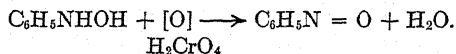
**Nitrosobenzene and Phenylhydroxylamine.** By the action of zinc dust and water on nitrobenzene, one oxygen atom is removed and nitrosobenzene results. This latter compound,



very readily combines with two hydrogen atoms so that, unless special precautions are taken, phenylhydroxylamine,  $\text{C}_6\text{H}_5\text{NHOH}$ , is the final product:



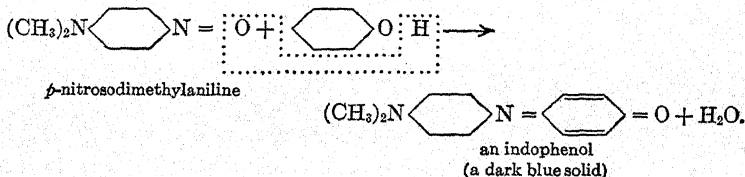
Phenylhydroxylamine can be oxidized to nitrosobenzene by the action of aqueous chromic acid, and this is perhaps the best method of preparing the nitroso compound:



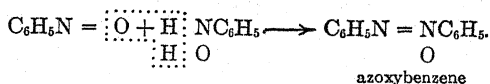
Phenylhydroxylamine undergoes a molecular rearrangement when treated with acids to give para aminophenol (p. 394).

Nitrosobenzene is a colorless, crystalline solid which melts at  $68^\circ$  to a blue-green liquid. Solutions of nitrosobenzene are also colored. It has been shown that in this case and with other nitroso compounds a colorless, dimolecular form (two molecules associated together) exists as well as the colored simple molecule. The crystalline nitrosobenzene is probably entirely the dimolecular form.

The nitroso group is very reactive, and nitroso compounds undergo condensation reactions with many substances containing an "active hydrogen" attached to a carbon atom. Since para nitrosodimethylaniline (p. 367) is more readily prepared than nitrosobenzene, and is more stable, its condensation reactions are of more importance than those of the parent substance. As an illustration, the condensation with phenol may be written:



**Azoxybenzene and Azobenzene.** The condensation of one molecule of nitrosobenzene and one molecule of phenylhydroxylamine produces azoxybenzene:



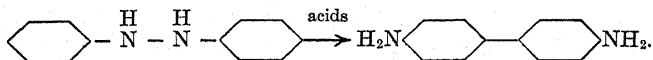
As the isolation of each of the two reactants in the above equation is somewhat difficult, it is more convenient to prepare azoxybenzene directly from nitrobenzene in one operation. By heating the nitro compound with potassium methylate ( $\text{CH}_3\text{OK}$ ), the reduction proceeds only as far as the nitroso and phenylhydroxylamine stage; these then condense rapidly in the alkaline medium, forming azoxybenzene. The potassium methylate is oxidized to potassium formate. Azoxybenzene is a bright yellow solid melting at  $36^\circ$ .

The oxygen atom of azoxybenzene is easily removed by heating the compound with iron filings and **azobenzene**,  $\text{C}_6\text{H}_5\text{N} = \text{NC}_6\text{H}_5$ , results. The more convenient and usual method of preparation of azobenzene is to reduce nitrobenzene with an alkaline solution of stannous chloride (sodium stannite). This reducing agent probably first forms azoxybenzene by the mechanism given above, and then reduces this substance to azobenzene. Azobenzene is a bright red solid (m.p.  $67^\circ$ ). It is the parent substance of a large class of compounds, some of which are important dyes (p. 381). Compounds which contain the grouping  $-\text{N} = \text{N}-$  between two benzene nuclei are named as derivatives of azobenzene; almost none of them are prepared from the parent compound azobenzene, however, which is therefore of little importance.

**Hydrazobenzene.** Azobenzene readily combines with two hydrogen atoms when treated with reducing agents; the product is hydrazobenzene,  $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$ . If vigorous reducing agents such as a metal-acid combination are employed, the hydrazobenzene is further reduced to aniline. Thus the primary amine is the final reduction product even of the condensed molecules of the azoxybenzene series:

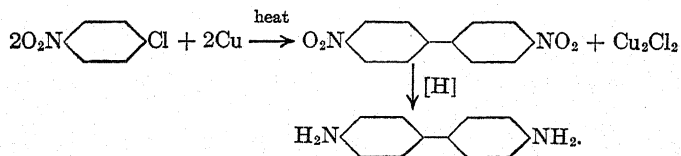


**Benzidine.** When hydrazobenzene is treated with mineral acids, it undergoes a remarkable *rearrangement*. The product is benzidine, a colorless solid melting at 128°:



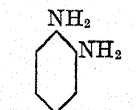
This diamino compound is a very valuable substance in the preparation of certain dyes. It is prepared on a large scale by reducing nitrobenzene to hydrazobenzene by the action of zinc dust and aqueous sodium hydroxide. The hydrazobenzene when treated with acid rearranges to benzidine.

**Structure of Benzidine.** The method of preparation of benzidine obviously tells us nothing about its structure. The presence of two primary amino groups is established by the formation of a di-diazonium salt with nitrous acid. On boiling this salt with alcohol, the  $\text{N}_2\text{Cl}$  group is replaced by hydrogen (p. 458), and diphenyl,  $\text{C}_6\text{H}_5\text{C}_6\text{H}_5$ , is formed. This proves that benzidine is a diaminodiphenyl, but leaves the position of the groups still uncertain. The synthesis of benzidine from para chloronitrobenzene proves that it is 4, 4'-diaminodiphenyl. This synthesis is not an industrial process; the steps are as follows:

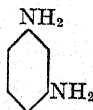


### THE DIAMINES

The diamino derivatives of benzene are known as the **phenylene diamines**. The nomenclature is peculiar and is based on the concept of  $\text{C}_6\text{H}_4\text{<}$  as a "phenylene group" analogous to  $\text{CH}_2\text{<}$ , the methylene group of the aliphatic series. The three isomeric phenylene diamines have the physical properties noted below:



ortho phenylene  
diamine  
b.p. 252°  
m.p. 102°



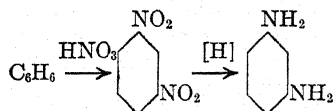
meta phenylene  
diamine  
b.p. 287°  
m.p. 62°



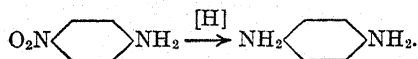
para phenylene  
diamine  
b.p. 267°  
m.p. 140°

All three substances are slightly soluble in cold water but soluble in warm water and a variety of organic solvents. They are easily oxidized, becoming darkly colored on standing in the air. They are weak bases of about the strength of aniline and will combine with one or two molecules of an acid to form salts. They react with nitrous acid to form diazonium salts, which then undergo condensation to complex compounds. For this reason the diamines are not used in the synthesis of other disubstituted benzenes.

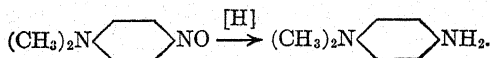
**Industrial Preparation and Uses.** The meta phenylene diamine is prepared by the complete reduction of meta dinitrobenzene, which, in turn, is prepared from benzene:



The ortho and para phenylene diamines are prepared from the corresponding nitroanilines by reduction. The *o*- and *p*-nitroanilines may be prepared by the method on page 370, or by treating ortho and para nitrochlorobenzenes with ammonia.



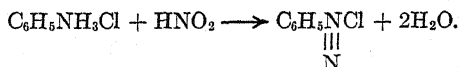
The diamines are used in the preparation of a variety of dyes and are among the important dye intermediates. Not only the diamines themselves but also the dimethyl derivatives are used. The latter are prepared by the reduction of the corresponding nitro or nitroso dimethylanilines. The para nitrosodimethylaniline is readily prepared from dimethylaniline (p. 367):



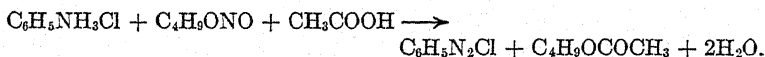
### THE DIAZONIUM SALTS

**Diazotization.** The synthesis of aromatic compounds is greatly facilitated by the easy conversion of aromatic primary amines into **diazonium salts**. These compounds are very reactive, and from them many different types of products may be prepared. The process of converting the salt of a **primary aromatic amine** into

the **diazonium salt** is called **diazotization**. It is usually carried out by dissolving the amine in dilute aqueous acid and adding a solution of sodium nitrite. It is necessary to keep the temperature low, as otherwise both the nitrous acid and the diazonium salt may decompose:



The aqueous solutions of diazonium salts are usually so unstable that it is not possible to obtain the solid salt by evaporation. Such crystalline salts, however, may be prepared by diazotization in glacial acetic acid and precipitation with ether, in which they are insoluble. In this case an organic ester of nitrous acid, such as **butyl nitrite**, is used instead of sodium nitrite:



The dry diazonium salts are easily detonated.

**Structure of Diazonium Salts.** The diazonium salts may be represented as  $\text{ArN}_2\text{X}$ , in which Ar is an aryl group, such as phenyl, and X, an acid group. In solution, they are dissociated into the ions  $\text{ArN}_2^+ + \text{X}^-$ . The formula  $\text{C}_6\text{H}_5 - \text{N} - \text{Cl}$  is usually pre-



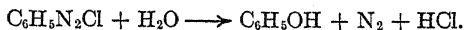
ferred to  $\text{C}_6\text{H}_5\text{N} = \text{N} - \text{Cl}$ . The substance,  $\text{C}_6\text{H}_5\text{N}_2\text{Cl}$ , is called **benzene diazonium chloride**. The reactions of a diazonium salt are thus essentially the reactions of the diazonium ion. This ion is very unstable and reactive and undergoes varied transformations which depend on the conditions.

The problem of the structure of the diazonium salts is the problem of the position of the positive charge on the diazonium ion. In other words, the location of an electron is involved. The two structures  $\text{C}_6\text{H}_5 : \overset{+}{\text{N}} :: \text{N} :$  and  $\text{C}_6\text{H}_5 : \text{N} :: \overset{+}{\text{N}} :$  clearly represent two *resonating structures* (p. 258). The ion is a resonating hybrid.

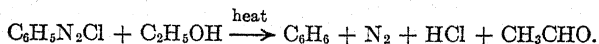
**Reactions of Diazonium Salts.** The following reactions of diazonium salts are of great synthetic value. Although they will be illustrated by considering benzene diazonium chloride, it is important to bear in mind that a *diazonium salt from any primary aromatic amine* will behave in the same manner.

(1) *The Replacement of  $N_2X$  by  $OH$ :*

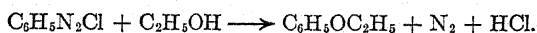
This is brought about by merely warming an aqueous solution of the diazotized amine. The solution should be strongly acid to avoid the coupling reaction between phenol and undecomposed diazonium salt, a reaction which is discussed on the next page.

(2) *The Replacement of  $N_2X$  by  $H$ :*

Some diazonium salts are converted to the corresponding hydrocarbon by heating them with ethyl alcohol.



This method is not general since very frequently an ether is formed:

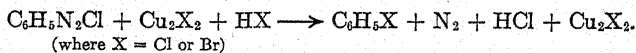


With benzene diazonium chloride a mixture of the hydrocarbon and ether is formed. The course of the reaction of diazonium salts with alcohols depends largely on the nature of the alcohol, the diazonium salt, and on the conditions of experiment.

Other reagents such as formic acid and sodium stannite (alkaline stannous chloride) are effective in replacing the  $N_2X$  group by hydrogen.

(3) *The Replacement of  $N_2X$  by Halogens:*

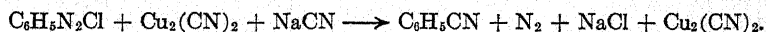
In this reaction the solution is kept as concentrated as possible and one mole of cuprous salt and a considerable amount of halogen acid are added. A complex compound between the cuprous salt and the diazonium salt is first formed and often precipitates. This slowly decomposes and yields the aryl halide and nitrogen:



The introduction of an iodine atom does not require the use of a cuprous salt. Hydrogen iodide or its salts may be used.

(4) *Replacement of  $N_2X$  by  $CN$ :*

This reaction takes place when sodium cyanide and cuprous cyanide are used:



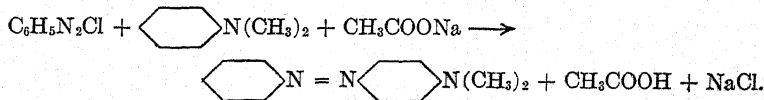
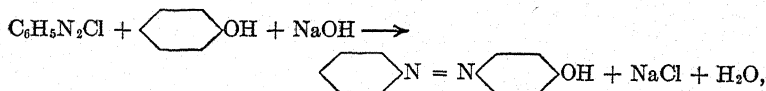
The preceding two reactions are often called the **Sandmeyer reaction**. If finely divided copper is used as the catalyst, the reaction is known as the **Gattermann reaction**.

**Phenylhydrazine,  $C_6H_5NHNH_2$ .** When an aqueous solution of benzene diazonium chloride is reduced, the hydrochloride of phenylhydrazine is formed:



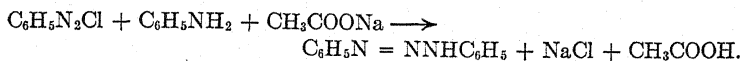
Stannous chloride in hydrochloric acid or sodium sulfite are the usual reducing agents employed. The free base can be prepared from the salt in the usual manner. Phenylhydrazine may be considered as the phenyl derivative of the inorganic base **hydrazine**,  $NH_2NH_2$ . It has been of great value in the laboratory because it reacts with ketones and aldehydes forming crystalline compounds called **phenylhydrazones**. These have proved very useful in the identification and isolation of ketones and aldehydes (p. 122). Indeed, the discovery of phenylhydrazine by Emil Fischer in 1875 enabled him to make great advances in our knowledge of the carbohydrates (p. 303).

**The Coupling of Diazonium Salts.** The usefulness of the diazonium salts is not exhausted with the replacement reactions we have just considered. This remarkable class of compounds is also the basis of one branch of the synthetic coal tar dye industry. The azo dyes (Chap. XXX) are all prepared by the so-called coupling of diazonium salts. This coupling reaction takes place when a *phenol* or *aryl amine* is treated with a diazonium salt solution. Sodium acetate, sodium carbonate, or sodium hydroxide is added to make the mixture less acid:



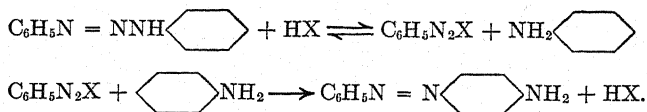
It will be noted, in the examples given above, that the coupling reaction has taken place in the para position. The ortho and para hydrogen atoms in phenols and tertiary amines are reactive and, therefore, the process takes place with these compounds. Hydro-

carbons with only a few exceptions will not couple with diazonium salts. If a primary or secondary aryl amine is used, the coupling takes place on the nitrogen atom.



On heating the resulting compound in weakly acid solution or with aniline hydrochloride, a rearrangement occurs, and a product is formed,  $\text{C}_6\text{H}_5\text{N} = \text{NC}_6\text{H}_4\text{NH}_2$ , which corresponds to that produced by direct para coupling in the case of the tertiary amine.

The mechanism of this process involves the hydrolysis of the diazoamino compound back to the diazonium salt and amine which then slowly couple the other way round. Thus:

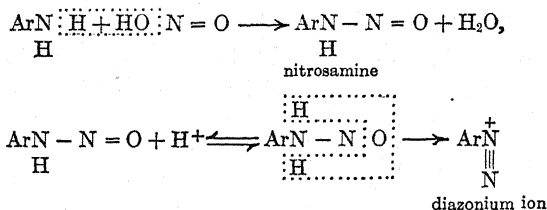


Ordinarily, the coupling of primary and secondary amines is carried out in slightly acid medium. Under these conditions direct para or ortho coupling occurs.

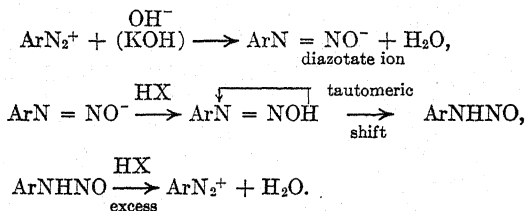
**Nomenclature of Azo Compounds.** The substances produced by coupling a diazotized aryl amine and a phenol or tertiary amine are derivatives of azobenzene. Thus, the product of the interaction of diazotized aniline and phenol is called *p*-hydroxyazobenzene; the compound from dimethyl aniline and benzene diazonium chloride is *p*-dimethylaminoazobenzene. The compound first formed in the coupling of aniline and diazotized aniline,  $\text{C}_6\text{H}_5\text{N}_2\text{-NHC}_6\text{H}_5$ , is known as diazoaminobenzene. In general, *diazo compounds* contain the grouping  $\text{ArN} = \text{N} - \text{Z}$ , where Ar is any aryl group and Z any group not linked through carbon to the nitrogen. The *azo compounds* contain the group  $-\text{N} = \text{N}-$  with a carbon to nitrogen linkage on both sides as in azobenzene itself.

**Mechanism of Diazotization and Coupling.** The process of diazotization may be better understood by comparing it with the action of nitrous acid on a secondary amine. In this case, it will be recalled, the one and only hydrogen atom of the amino group is replaced by a nitroso group. A similar compound (a nitrosamine) is probably first formed in the diazotization of a primary

amine, but an excess of mineral acid converts it at once into the diazonium salt. The reactions may be formulated thus:

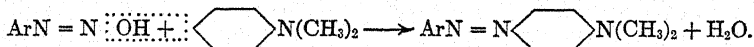
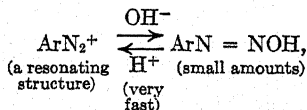


It is very difficult to prove that the reaction takes the course pictured above, but the nitrosamines,  $\text{ArNHNO}$ , can be prepared by the action of dilute alkali on the diazonium salts, followed by cautious acidification. Excess of mineral acid indeed does convert the nitrosamine into the diazonium salt so that a complete cycle may be carried out:



The diazotates are the salts of the unstable acid  $\text{ArN} = \text{NOH}$ ; the salts are stable substances and are usually known in two forms. The existence of the two isomers has been explained on the basis of geometrical isomerism.

The coupling reactions of the diazonium salts proceed through the formation of the compound  $\text{ArN} = \text{NOH}$ . Written as an ionic reaction, the equations are:




These equations enable one to picture more readily the formation of an azo compound from a diazonium salt. The diazonium ion predominates in the equilibrium in even neutral solutions because of its relative stability due to the resonance energy. The function of the sodium acetate which must be added to bring about the coupling with amines or the alkali which must be present in the case of the phenols is readily explained. These inorganic reagents regulate the hydroxyl ion concentration of the aqueous solution, and thus provide a continually sufficient concentration of the reactive  $\text{C}_6\text{H}_5\text{N} = \text{NOH}$ . The less acid the solution the more rapid the coupling; at the acidity

of acetic acid (obtained by adding an excess of sodium acetate), the concentration of the reactive  $\text{ArN} = \text{NOH}$  must be very small, but this fact is counterbalanced by the great speed with which it reacts with the tertiary amine.

### QUESTIONS AND PROBLEMS

1. Write structural formulas for: sulfanilic acid; diphenyl amine; 1, 2-dinitrobenzene; 3, 4, 6-trinitroaniline; *p*-nitrosophenol; phenylhydroxylamine; *p*-amino-azobenzene; meta phenylene diamine.

2. Outline the steps in the synthesis of the following from the coal tar crudes: acetanilide, a mixture of ortho and para toluidines, para nitrosodimethylaniline, all three nitroanilines, para phenylene diamine.

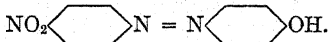
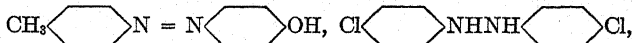
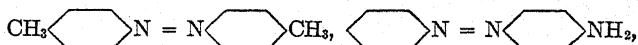
3. How would you distinguish between  $\text{C}_6\text{H}_5\text{NHCH}_3$  and  $\text{CH}_3$ -- $\text{NH}_2$ ? Between  $(\text{CH}_3)_2\text{NC}_6\text{H}_5$  and  $(\text{CH}_3)_2\text{C}_6\text{H}_4\text{NH}_2$ ?

4. In what respects is triphenyl amine different from triethyl amine? How is it prepared?

5. How would you separate by chemical methods a mixture of picric acid, dinitrobenzene, and para toluidine? These substances are all crystalline solids soluble in organic solvents and only slightly soluble in pure water.

6. In what respects are the nitrophenols, nitroaryl halides, and nitroanilines peculiar?

7. Name and outline the syntheses of the following compounds:

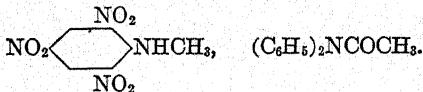
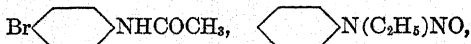


8. Devise methods for preparing each of the substances listed in question 1.

9. State clearly the experimental facts which establish that benzidine is a diamino derivative of diphenyl.

10. Write equations illustrating the action of the following reagents on benzene diazonium chloride: ethyl alcohol, cuprous bromide and hydrobromic acid, cuprous cyanide and potassium cyanide, an alkaline solution of phenol.

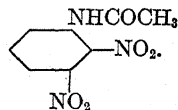
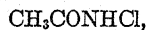
11. Predict the solubility in dilute hydrochloric acid of the following substances which are insoluble in water:



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12. Compare the action of nitrous acid on:  $\text{CH}_3\text{NH}_2$ ,  $\text{C}_6\text{H}_5\text{NH}_2$ ,  $\text{C}_6\text{H}_5\text{-NHCH}_3$ ,  $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$ ,  $\text{CH}_3\text{CONH}_2$ , and urea.

13. Predict whether the following substances will be more or less basic than aniline:



14. Predict the products of the following reactions:  $\text{CH}_3\text{C}_6\text{H}_5(\text{NO}_2)_2$ -1, 2, 3 +  $\text{NH}_3$  (high temperature);  $\text{CH}_3\text{C}_6\text{H}_5\text{NO}_2\text{Cl}$ -1, 3, 4 +  $\text{CH}_3\text{NH}_2$ ;  $\text{C}_6\text{H}_4(\text{NO}_2)_2$ -1, 4 +  $\text{CH}_3\text{NH}_2$  (high temperature).

## CHAPTER XXI

### POLYHYDROXY COMPOUNDS AND AMINOPHENOLS

Polyhydroxy compounds and aminophenols are considered together in this chapter since in some of their reactions they are similar. They find wide use as photographic developers and as dye and drug intermediates.

#### POLYHYDROXY COMPOUNDS

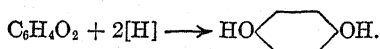
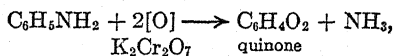
**General Characteristics.** The derivatives of benzene with two or more hydroxyl groups attached to the ring resemble phenol in their chemical behavior. They are very weak acids, and give a characteristic color with ferric chloride. As would be expected from the number of hydroxyl groups, they are readily soluble in water. The isomeric di- and trihydroxybenzenes are listed below together with their physical properties:

#### ISOMERIC DI- AND TRIHYDROXYBENZENES

NAME	FORMULA	BOILING POINT	MELTING POINT	SOLUBILITY GRAMS PER 100 GRAMS OF WATER AT 20°
Pyrocatechol ( <i>o</i> -Dihydroxybenzene)	$C_6H_4(OH)_2(1, 2)$	245°	105°	24
Resorcinol (Resorcin) ( <i>m</i> -Dihydroxybenzene)	$C_6H_4(OH)_2(1, 3)$	277°	110°	147
Hydroquinone ( <i>p</i> -Dihydroxybenzene)	$C_6H_4(OH)_2(1, 4)$	286°	171°	6.5
Pyrogallol (1, 2, 3-Tri- hydroxybenzene)	$C_6H_3(OH)_3(1, 2, 3)$	309°	134°	60
Phloroglucinol (1, 3, 5-Tri- hydroxybenzene)	$C_6H_3(OH)_3(1, 3, 5)$		219°	very soluble
1, 2, 4-Trihydroxybenzene	$C_6H_3(OH)_3(1, 2, 4)$		141°	—

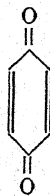
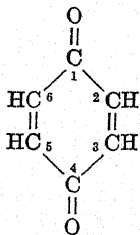
**Preparation of Hydroquinone.** Hydroquinone,  $C_6H_4(OH)_2$  (1, 4), is prepared by a very peculiar method. When aniline is oxidized with potassium dichromate and sulfuric acid, a yellow,

volatile solid, quinone or benzoquinone,  $C_6H_4O_2$ , is formed. This compound on reduction with sulfur dioxide yields hydroquinone. In the preparation of hydroquinone on a large scale no effort is made to separate the intermediate compound; it is at once distilled with steam from the reaction mixture and reduced with iron and acid. The hydroquinone is obtained as a crystalline mass on concentrating the solution.



Hydroquinone is a colorless, crystalline solid which melts at  $171^\circ$  to a liquid which boils at  $286^\circ$ . It may be purified by crystallization or distillation under diminished pressure. It finds wide use as a photographic developer.

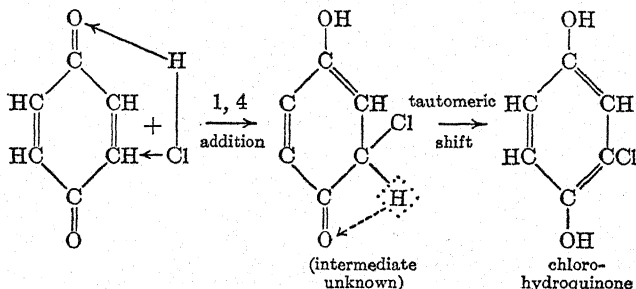
**Quinone (1, 4-Benzoquinone).** If we examine the intermediate substance, quinone, we find that it is a yellow, crystalline solid (m.p.  $116^\circ$ ) with a penetrating odor. It does not behave like an aromatic compound. On the contrary, it shows the typical reactions of an olefin hydrocarbon on the one hand and of an aliphatic ketone on the other. For example, it combines with four atoms of bromine to form a tetrabromide, and reacts with hydroxylamine forming a dioxime. Taking into account these facts and its easy conversion into para dihydroxybenzene (whose structure is definitely established by other syntheses), we can write the following formula with considerable confidence. (The outline formula on the right is frequently employed.)



It will be noted that in this compound the double linkages are indicated as being definitely in the 2, 3 and 5, 6 positions, and that, unlike benzene, and its derivatives, two of the six carbon atoms

are attached to a divalent atom (oxygen). Although quinone is formed by the oxidation of an aromatic compound and passes into a member of this class on reduction, it is itself *not a typical aromatic substance*. Quinone is an unsaturated, cyclic ketone, — an alicyclic compound.

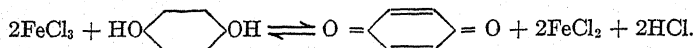
It will be noted that quinone contains a conjugated system of double linkages. Unlike benzene, however, the conjugated system is not complete and symmetrical, but has two oxygen atoms at the ends. In many of its reactions quinone is very similar to the  $\alpha$ ,  $\beta$ -unsaturated ketones discussed in Chap. XVI. Carbonyl reagents react both normally with the carbonyl group (1, 2 addition) and also abnormally, yielding 1, 4 addition products, as in the case of the  $\alpha$ ,  $\beta$ -unsaturated ketones (p. 292). The reaction of hydrogen chloride and quinone is of the latter type; a chlorohydroquinone is the product.



**Quinhydrone.** When hydroquinone and quinone are present in solution they form the very dark brown molecular compound, quinhydrone,  $C_6H_4O_2 \cdot C_6H_4(OH)_2$ . This may be obtained in greenish black crystals by evaporation of the solution. The compound is usually prepared by the partial oxidation of hydroquinone. In solution it is largely dissociated into its components, quinone and hydroquinone. The speed of the dissociation is so rapid that no characteristic reactions of quinhydrone are known; it behaves chemically like a mixture of quinone and hydroquinone. The exact nature of the valence forces which hold the two molecules together in quinhydrone is unknown. Other so-called molecular compounds are known; for example, the addition compounds of picric acid and the aromatic hydrocarbons (p. 362).

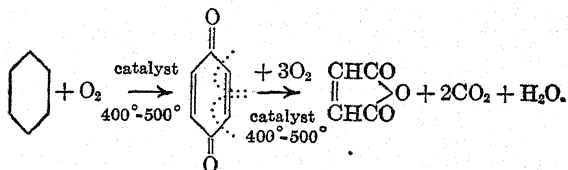
**Reversibility of the Reduction of Quinone.** The change from quinone to hydroquinone can easily be reversed in acid solution by treating hydroquinone with an oxidizing agent. The reduction of quinone to hydroquinone and the re-oxidation of the latter are extraordinarily rapid processes and are strictly reversible. This is one of the relatively few oxidation and reduction reactions of

organic chemistry which is rapid and reversible like the oxidation and reduction of inorganic ions.



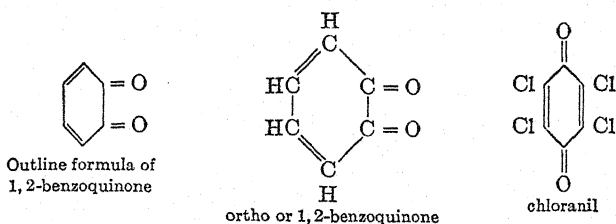
If a platinum wire is dipped into a solution of quinone and hydroquinone in a conducting solvent (*e.g.*, dilute acid), a definite electrical potential is developed on the wire. Such a system will serve as one half of an electric battery provided a conducting liquid connects it with another "half cell" (for example, a piece of zinc dipping in dilute acid). The potential of the inert electrode (platinum wire) is found to depend in a precise way on the relative amounts of quinone and hydroquinone in the solution. Other quinones (see below) and their corresponding hydroquinones, certain dyes and their reduction products, and a few other classes of organic compounds show this same behavior. Mixtures of reduced and oxidized inorganic ions (*e.g.*, ferrous and ferric) usually develop a potential in the same way, but most combinations of organic systems *do not*. The quinone-hydroquinone system is a representative of a special class in which there is an easily reversible oxidation-reduction relationship.

**Catalytic Oxidation of Benzene.** When a mixture of benzene vapor and air is passed over certain metallic oxides heated to 400°–500°, maleic anhydride is the chief product. As previously mentioned (p. 286), this is the modern industrial method of preparing these compounds. The reaction appears to proceed through the intermediate formation of benzoquinone, which is then further oxidized to maleic acid. Indeed, under certain conditions, benzoquinone can be isolated from the product. It has been known for a long time that with certain oxidizing agents benzoquinone is oxidized to maleic acid:



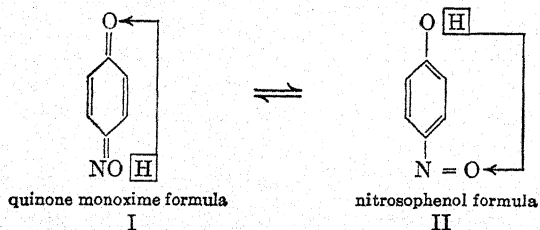
**Other Quinones.** The substance referred to above as quinone is more correctly called 1, 4- or para benzoquinone. The nomenclature shows that the oxygen atoms are in the 1, 4 or para position and that it is derived from benzene. One other benzoquinone is known; this is the 1, 2- or ortho benzoquinone, which is formed by oxidizing the corresponding dihydroxy compound. A great variety of substituted 1, 4 and 1, 2-benzoquinones are known, as

well as quinones related to other polycyclic aromatic hydrocarbons (p. 458). **Chloranil** or tetrachloro-para-benzoquinone (m.p. 290°) is a yellow solid formed by treating a great variety of organic compounds, such as aniline or phenol, with potassium chlorate and hydrochloric acid (a chlorinating and oxidizing mixture).



As might be expected meta quinones are unknown, since it is impossible to write a formula for such a compound without having free linkages or a bridge across the ring. The oxidation of meta hydroxy compounds proceeds readily, but yields complex products.

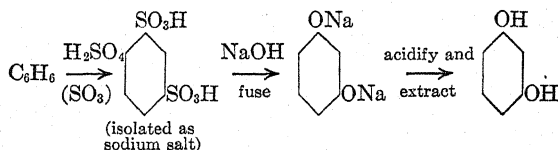
**Tautomerism of Quinone Monoxime.** The diketonic nature of quinone is demonstrated, among other reactions, by the formation of the dioxime, which behaves in every way as a ketonic oxime should. It is also possible to obtain a monoxime from quinone by the action of hydroxylamine. This substance would be expected to have the formula I, below. It is identical, however, with the product obtained by the action of nitrous acid on phenol or by the decomposition of nitrosodimethylaniline (p. 367). Judged by this method of formation, it should have formula II. It is evident that we are here dealing with a tautomeric substance as in the case of cyanic acid (p. 253).



Whether the one substance which is known is to be represented by formula I or II is still uncertain; it is usually called *p*-nitroso-

phenol, although the name quinone monoxime is also employed. It is a light yellow, crystalline compound melting at  $126^{\circ}$ . It dissolves in organic solvents with a greenish color. It is a weak acid, and therefore readily dissolves in aqueous alkali, forming a brown solution of the sodium salt.

**Preparation of Resorcinol**,  $C_6H_4(OH)_2$ -1, 3, is prepared industrially by alkaline fusion of the corresponding disulfonic acid. Starting with benzene, the steps involved are the following:



It is also prepared by the fusion of meta bromobenzenesulfonic acid.

It is a peculiar fact that ortho and para bromosulfonic acids and para benzenedisulfonic acid on fusion with alkali yield resorcinol. Obviously, at the high temperatures of fusion, a rearrangement occurs. This fact is significant, since it demonstrates that fusion reactions are often unreliable in determining the structure of aromatic compounds.

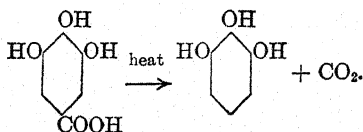
**Hexylresorcinol**,  $C_6H_3(OH)_2CH_2CH_2CH_2CH_2CH_2CH_3$  (1, 3, 4), (the numbers refer to the positions of the groups), is a derivative of resorcinol which has been found to have valuable antiseptic properties, and is now manufactured for this purpose.

**Pyrocatechol**. The ortho dihydroxybenzene,  $C_6H_4(OH)_2$  (1, 2), is known as pyrocatechol or catechol. It can be prepared from ortho chlorophenol by hydrolysis of the compound in an aqueous solution of sodium and strontium hydroxides in the presence of copper. It is easily oxidized in alkaline solution, yielding complex products. When oxidized with silver oxide under special conditions pyrocatechol yields ortho benzoquinone.

The pyrocatechol grouping occurs in a great variety of natural products; sometimes with both phenolic groups free, sometimes partially methylated, and sometimes combined with a methylene group. A number of such natural products, including the substance lignin present in wood, will be discussed in the following chapters.

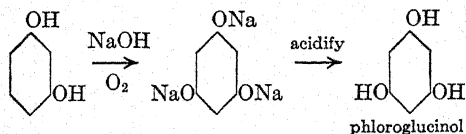
**Guaiacol**,  $C_6H_4(OCH_3)(OH)$  (1, 2), is the monomethyl ether of catechol. It was first obtained by the destructive distillation of gum guaiacum (a resin), and occurs in large quantities in wood tar. It can be synthesized from phenol or benzene by a variety of processes. Guaiacol is a low-melting, colorless solid (m.p.  $28^\circ$ ) with a characteristic, pleasant odor. It is used in medicine and pharmaceutical preparations. It can be converted into catechol by boiling with hydrobromic or hydriodic acid.

**Pyrogallol from Gallic Acid.** Pyrogallol, or pyrogallie acid,  $C_6H_3(OH)_3$  (1, 2, 3), is one of the few aromatic compounds which is *not prepared from coal tar*. It has been synthesized from benzene in the laboratory, but the process is too difficult and expensive to be used industrially. **Gallic acid**,  $C_6H_2(OH)_3COOH$ , is a substance which is readily prepared on a large scale from tannic acid (p. 424). On heating, gallic acid loses carbon dioxide and forms pyrogallol:



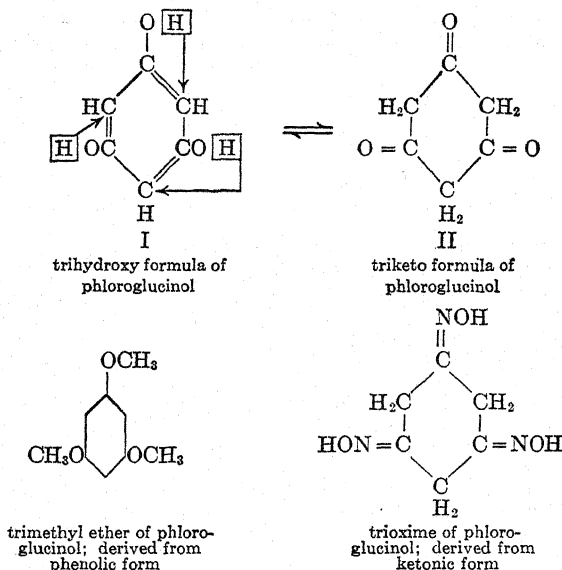
This trihydroxybenzene thus owes its importance to the fact that it can be readily obtained from a natural product (tannic acid). It is used as a developing agent and as a dye intermediate. Its alkaline solutions are very easily oxidized even by atmospheric oxygen. They are often used as an absorbent for oxygen in gas analysis.

**Phloroglucinol.** Symmetrical trihydroxybenzene,  $C_6H_3(OH)_3$ -1, 3, 5, is called phloroglucinol. It may be prepared by the fusion of the sodium salt of 1, 3, 5-benzene trisulfonic acid with sodium hydroxide. It is also prepared by fusing resorcinol with sodium hydroxide in air. In this reaction oxygen of the air is involved:



Phloroglucinol is a tautomeric substance; some of its reactions correspond to those expected from a trihydroxybenzene, while others indicate that it is a cyclic triketone. For example, when treated with diazomethane (p. 248), it forms a trimethyl ether; such a reaction is characteristic of the phenols. On the other

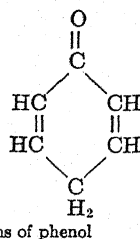
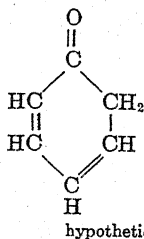
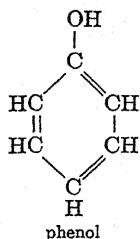
hand, when treated with hydroxylamine it forms a trioxime. This latter reaction would seem to indicate that phloroglucinol was to be represented by formula II instead of I:



An inspection of the two tautomeric formulas I and II shows that I is the enolic form of II. We are evidently here concerned with a case of keto-enol tautomerism discussed in Chap. XIII. No one has yet succeeded, however, in isolating isomeric forms of phloroglucinol corresponding to the two formulas. In solution or in the molten state both forms are probably present in equilibrium. There is no clear evidence to enable us to decide whether the solid is to be represented by formula I or II.

It is particularly interesting that the tautomeric shift of phloroglucinol involves the change from an aromatic structure to an alicyclic structure. This was also the case in the tautomerism of nitrosophenol (quinone monoxime). It is evident that in some instances, the distinction between aromatic compounds and alicyclic compounds may be bridged by a shift of one or more hydrogen atoms. The hydroxy derivatives of benzene are thus to be regarded as the enolic form of certain alicyclic ketones. In the case of the monohydroxy compounds (*e.g.*, phenol), there is no evidence of the existence of any of the ketonic forms. Phenol, for example,

does not form an oxime when treated with hydroxylamine. One of the most striking characteristics of aromatic compounds is that the hydroxyl derivatives are stable in the *enolic* form.

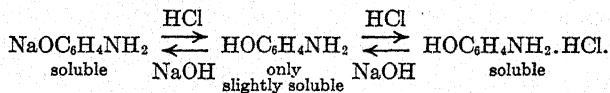


The alkylation of the potassium salt of phloroglucinol with methyl iodide takes place in somewhat the same manner as the alkylation of acetoacetic ester or malonic ester. The alkyl group becomes attached to carbon instead of oxygen. In this way a hexamethyl derivative of formula II can be prepared.

**Polyhydroxy Aromatic Compounds in Nature.** The hydroxy derivatives of benzene are widely distributed in the plant world, often as glycosides (p. 307) in which the phenolic group is attached to a glucose or other sugar molecule. A number of more or less complicated substances derived from the polyhydroxy compounds are found in the tannins (p. 425). Pyrocatechol, hydroquinone, and phloroglucinol have been isolated as glucosides from many species of plants. The glucoside of hydroquinone, known as *arbutin*, and is very common in the plant kingdom.

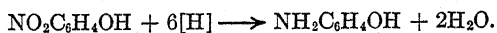
#### AMINOPHENOLS


The aminophenols are both aryl amines and phenols and give the characteristic reactions of both classes of substances. They are *amphoteric* like aluminum hydroxide, forming *salts with both acids and bases*. These salts are more soluble in water than the substances themselves:



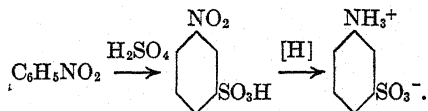
The solutions of the sodium salts are easily oxidized and are, therefore, not readily kept without change. The melting points of the three isomeric phenols are: ortho 170°, meta 123°, para 184°.

**The Preparation of Para Aminophenol.** This compound is important not only as a photographic developer but also as a dye intermediate, and is used in the synthesis of several drugs. There are a number of methods of preparing para aminophenol; the one most commonly employed is the reduction of para nitrophenol (p. 361).

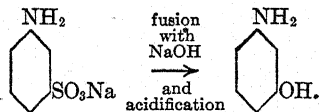


One fairly important drug is a derivative of *p*-aminophenol. This is **phenacetin**,  $\text{CH}_3\text{CONH}$    $\text{OC}_2\text{H}_5$ . It is an antipyretic superior in its action to acetanilide; the close relationship of the two compounds is evident. Phenacetin may be prepared from *p*-aminophenol by ethylating the sodium salt with ethyl chloride and then acetylating the para ethoxy aniline (phenetidine) thus produced.

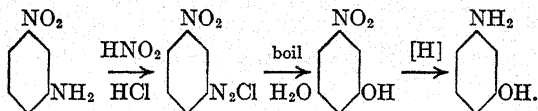
**Meta Aminophenol.** This compound is not used as a photographic developer but is a **dye intermediate**. Its preparation illustrates the general methods of obtaining meta compounds. The nitro group orients meta; therefore, if we introduce another substituent directly into nitrobenzene, a meta compound will be the product. On reduction we will then have a meta amino compound. **Metanilic acid**,  $\text{HO}_3\text{SC}_6\text{H}_4\text{NH}_2$  (an isomer of sulfanilic acid), is prepared in this way:



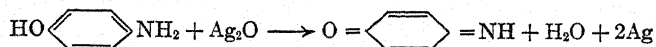
The sodium salt of metanilic acid on fusion with sodium hydroxide and subsequent acidification of the reaction mixture, yields meta aminophenol:



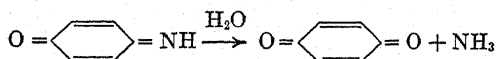
Another method of preparing meta aminophenol is from meta nitroaniline (p. 369). The amino group may be replaced by hydroxyl through the formation of the diazonium salt (p. 379). The meta nitrophenol is then reduced to the meta aminophenol.



**Quinonimine.** When para aminophenol is carefully oxidized by silver oxide, it loses two hydrogen atoms to form quinonimine:

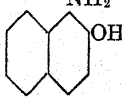


Like quinone-hydroquinone, quinonimine-aminophenol forms a reversible oxidation reduction system. Quinonimine is, however, very unstable. In the presence of dilute acids, it rapidly forms 1, 4-benzoquinone:

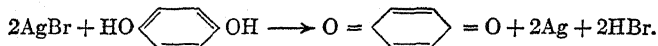


**Photographic Developers.** A number of aminophenols and polyhydroxy derivatives of benzene are used as photographic developers. All these compounds are easily oxidized in alkaline solution. Therefore, their alkaline solutions are reducing agents and slowly reduce silver halide to metallic silver. This is the fundamental reaction involved in the development of a photographic plate, and these organic reducing agents are used widely as photographic developers. It is impossible to write equations representing the organic chemistry of this process as the oxidation products are complicated and numerous. In general, however, it may be noted that all the organic developers have two OH

#### PHOTOGRAPHIC DEVELOPING AGENTS

SCIENTIFIC NAME	FORMULA	TRADE NAME
<i>p</i> -Aminophenol hydrochloride	$\text{HOC}_6\text{H}_4\text{NH}_2 \cdot \text{HCl}$	Rodinal
<i>p</i> -Methylaminophenol sulfate	$\text{HOC}_6\text{H}_4\text{NHCH}_3 \cdot \text{H}_2\text{SO}_4$	Metol
2, 4-Diaminophenol hydrochloride	$\text{HOC}_6\text{H}_3(\text{NH}_2)_2 \cdot \text{HCl}$	Amidol
<i>p</i> -Aminosaligenin hydrochloride	$\text{HOC}_6\text{H}_3(\text{CH}_2\text{OH})\text{NH}_2 \cdot \text{HCl}$	Edinol
<i>o</i> -Methylaminophenol	$\text{HOC}_6\text{H}_4\text{NHCH}_3 \cdot \text{HCl}$	Ortol
Sodium 1-amino-2-naphthol-6-sulfonate	$\text{NaO}_3\text{S}$ 	Eikonogen
Hydroquinone	$\text{HOC}_6\text{H}_4\text{OH}$	Hydroquinone
Pyrogallol	$\text{HOC}_6\text{H}_3(\text{OH})_2$	Pyro

groups, or an OH and an  $\text{NH}_2$  group in the ortho or para position of the benzene ring. As we have seen such compounds can lose a pair of hydrogen atoms and change into a quinoid form. Undoubtedly, the first step in the developing process is a **dehydrogenation** of the developer. We may write a somewhat hypothetical equation for the first step as follows:



Some of the organic substances which are used as developers are given on p. 395. A few of these have already been discussed.

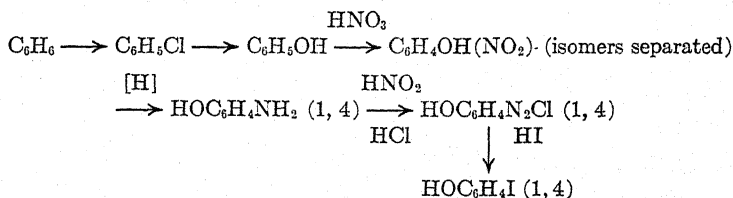
#### AROMATIC SYNTHESSES

Having now considered a variety of classes of aromatic compounds and surveyed the more important synthetic methods, we are in a position to apply this knowledge to new problems. We shall illustrate such applications by outlining the synthesis of a few compounds. In working out synthetic problems in this branch of organic chemistry, the same general principles apply as in aliphatic chemistry (Chap. VII, p. 141). The chemist must have a knowledge of the various types of compounds and the more important general methods of synthesizing each. In aromatic chemistry, particular care must be taken to insure that the proposed method will place the groups in the proper positions of the ring. The rules of orientation are here invaluable. The fundamental raw material is always coal tar; from this the coal tar crudes, — benzene, toluene, the xylenes, phenol, naphthalene, and anthracene, — can be isolated.

We may divide the syntheses into two groups according to whether (1) an ortho or a para compound is desired or (2) a meta compound is the goal. It will be seen from the examples below that even the synthesis of rather unusual derivatives of benzene is eventually based on a few well-known intermediates which are different in the two cases. As in aliphatic chemistry, one should endeavor to master the general principles and not attempt to commit the steps to memory. Each new problem should be solved by working out each step in the process *beginning with the last step*.

## EXAMPLES OF THE SYNTHESIS OF A PARA COMPOUND

**The Preparation of Para Iodophenol from Benzene.** In outlining a solution of this problem, it is first recalled that an iodine atom can not usually be directly introduced into the benzene ring; the diazonium replacement reaction, however, can be employed (p. 379). This requires a primary amine which in turn is prepared from a nitro compound. The hydroxyl group orients ortho and para, and, therefore, direct nitration puts the second group in the desired position.



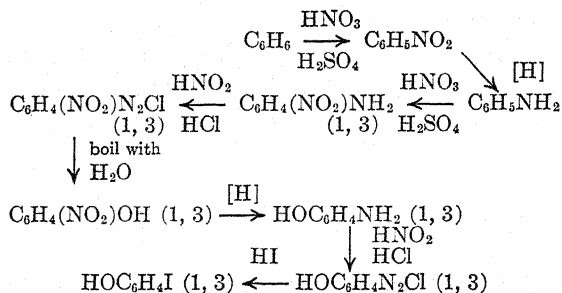
The relative position of two or more groups should always be shown in each step either by numbers in parenthesis or, better, by writing the hexagonal formula.

**The Preparation of Para Di-iodobenzene from Benzene.** This problem is very similar to the first except that para nitroaniline is prepared (p. 370) instead of para nitrophenol. The diazotization of this amine and the replacement reaction yield para nitroiodobenzene. From this point the synthesis is identical with the one just outlined. Para nitroiodobenzene could also be formed by direct nitration of iodobenzene which in turn is prepared from aniline through the Sandmeyer reaction or by the action of nitric acid and iodine on benzene (p. 342). *Di-iodobenzene can not be prepared from  $\text{C}_6\text{H}_4(\text{NH}_2)_2$  (see p. 377).*

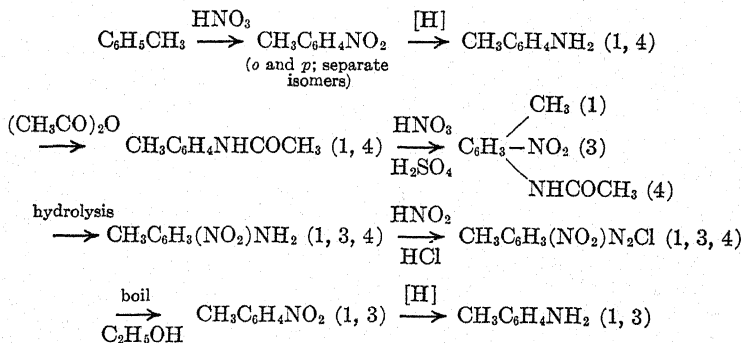
## EXAMPLES OF META SYNTHESSES

**Meta Nitroaniline and Meta Aminophenol.** These compounds are the basis of the synthesis of many meta compounds. The first is prepared either by the nitration of aniline (p. 369) or more usually by the partial reduction of meta dinitrobenzene. The reduction of one nitro group of the dinitro compound is accomplished by using ammonium sulfide (p. 369). Two methods of preparing meta aminophenol have already been considered (p. 394).

**The Preparation of Meta Iodophenol from Benzene.** The steps in the solution of this problem are as follows:



**Preparation of Meta Toluidine from Toluene.** The starting point in this case is toluene, but some special device must be employed to put the amino group in the meta position since the methyl group orients ortho and para. This is done by first introducing the acetylamino group in the para position, and subsequently removing it. Since the  $\text{NHCOCH}_3$  group has a more powerful orienting influence than a methyl group (p. 345), the entering group takes the desired position. This is a very good illustration of the importance of a knowledge of the relative directing power of various groups. The steps are as follows:

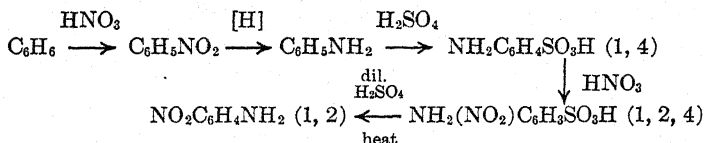


#### EXAMPLES OF ORTHO SYNTHESSES

Under the illustrations of para syntheses, we have seen that in one step a mixture of ortho and para isomers is obtained. Generally, in designing a scheme for an ortho synthesis, the ortho isomer is separated and subjected to the necessary reactions. Sometimes

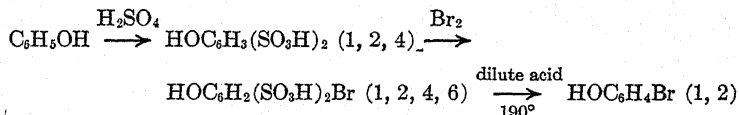
the proportion of ortho isomer obtained is too small to be of preparative value, and in these cases other methods must be devised. The following syntheses illustrate a method sometimes successful.

**Preparation of Ortho Nitroaniline from Benzene.**

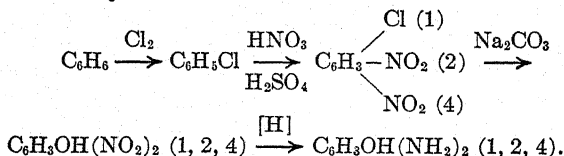


It should be noticed that the sulfonic acid group blocks the para position (sulfanilic acid), and, therefore, ortho substitution occurs. The sulfonic acid group is removed at the end by heating with dilute sulfuric acid (p. 349).

**Preparation of Ortho Bromophenol.** Since the monobromo compounds of phenol cannot be made directly, the ortho and para positions in phenol are blocked by sulfonic acid groups. On bromination the second ortho position is substituted.



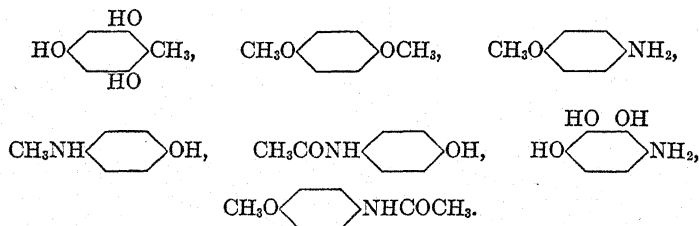
**Preparation of 2, 4-Diaminophenol from Benzene.** The industrial preparation of this compound (the photographic developer, amidol) illustrates how advantage may be taken of the reactive halogen in the nitro chlorobenzenes (nitro groups ortho and para). The steps in the synthesis are:



**QUESTIONS AND PROBLEMS**

1. Outline the steps in the preparation of the following from coal tar: hydroquinone, resorcin, *m*-aminophenol, phenacetin, phloroglucinol.
2. What is the fundamental reaction of an organic photographic developer? What do you think would happen if a solution of a photographic developer was warmed with an ammoniacal solution of silver nitrate?
3. Is quinone an aromatic compound? What facts indicate that it is an unsaturated diketone?

4. Discuss the tautomerism of nitrosophenol and phloroglucinol.
5. In what reactions is 2, 4-dinitrochlorobenzene different from chlorobenzene? What practical advantage is taken of this difference? Illustrate with several examples.
6. Predict the solubility in pure water, dilute hydrochloric acid, and dilute sodium hydroxide of the following crystalline compounds (a compound with a solubility of less than 1 per cent may be considered as insoluble):



If the compound is soluble in water, indicate whether or not salt formation would take place on the addition of hydrochloric acid or sodium hydroxide.

7. Which of the substances listed in question 6 do you think might reduce silver bromide if employed in an alkaline solution?
8. Devise three methods of preparing ortho nitro phenol and para amino-phenol.
9. Outline the steps in the synthesis of the following from coal tar crudes: para iodophenol, meta iodophenol, meta bromoaniline, para iodotoluene, para chlorophenol, meta bromotoluene, meta dibromobenzene, and para dibromobenzene (without the use of bromine), 1, 3, 4-tribromobenzene.
10. Predict the products of the following reactions:
  - (a)  $\text{HOC}_6\text{H}_4\text{N}=\text{NC}_6\text{H}_5$ -1, 4 +  $\text{SnCl}_2 + \text{HCl}$ .
  - (b)  $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_3$ -1, 4 +  $\text{HI}$ ; (c) hydroquinone + dimethyl sulfate + alkali.

## CHAPTER XXII

### AROMATIC ALDEHYDES AND KETONES

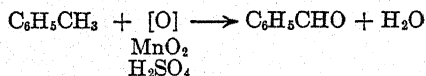
#### AROMATIC ALDEHYDES

It is usual to limit the term aromatic aldehyde to those compounds in which the aldehyde group is directly attached to the aromatic nucleus. In most respects aromatic aldehydes are similar to the aliphatic compounds considered in Chap. VI, but there are a few important differences. These may be best illustrated by first considering in detail the simplest aromatic aldehyde which is also the most important from the industrial standpoint.

**Benzaldehyde,  $C_6H_5CHO$ .** This aldehyde (b.p.  $180^\circ$ ) is much used in the synthesis of compounds which contain aromatic groups. It is also employed as a perfume and flavoring material under the name of "oil of bitter almonds." Before the development of the coal tar dye industry it was prepared by crushing bitter almonds with water. These nuts contain a glucoside, **amygdalin**, and an enzyme which causes its hydrolysis to glucose, hydrocyanic acid, and benzaldehyde.

Benzaldehyde is now prepared industrially from toluene directly or from its chlorination products, benzyl chloride,  $C_6H_5CH_2Cl$  or benzal chloride,  $C_6H_5CHCl_2$  (p. 342).

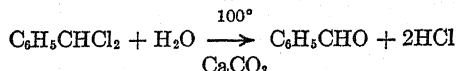
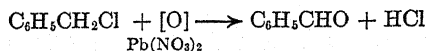
The oxidation of toluene to benzaldehyde is brought about by the use of manganese dioxide and sulfuric acid with the addition of copper sulfate as catalyst:



It is obvious that the production of an aldehyde by oxidation procedure must involve the use of special oxidizing agents and controlled conditions, as otherwise the aldehyde will be further oxidized to the corresponding acid.

The conversion of benzyl chloride to benzaldehyde is accomplished by oxidation with an aqueous solution of lead or copper

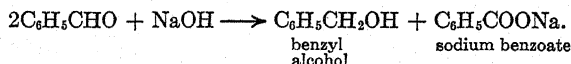
nitrates. Benzal chloride is readily transformed into benzaldehyde by boiling with water containing a small amount of alkali:



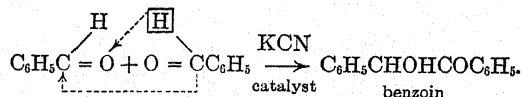
The above methods are applicable to the preparation of other aromatic aldehydes from the corresponding methyl compounds.

**Characteristics of Aromatic Aldehydes.** Benzaldehyde and its derivatives are similar to those aliphatic aldehydes which have *no hydrogen in the alpha position*, for example,  $(\text{CH}_3)_3\text{C}-\text{CHO}$ , and  $\text{HCHO}$  (compare p. 129). They give the fuchsine test, reduce ammoniacal silver nitrate solution, combine with sodium bisulfite, hydrocyanic acid, and the Grignard reagent; they readily form oximes and phenylhydrazones.

Because of the absence of an alpha hydrogen atom, they do *not* undergo an aldol condensation nor resinify when treated with alkali. Instead they undergo the Cannizzaro reaction (p. 128):



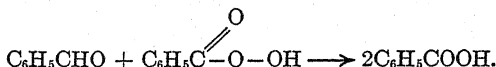
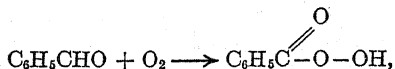
A characteristic reaction of many aromatic aldehydes is the **benzoin condensation**. This is brought about by warming the aldehyde with a solution of potassium cyanide; the cyanide ion is the specific catalyst for this process. A graphical equation for the formation of benzoin,  $\text{C}_6\text{H}_5\text{CHOHCOC}_6\text{H}_5$ , from benzaldehyde will illustrate the reaction:



Unlike the aliphatic aldehydes, the aromatic aldehydes do not form polymers when treated with acids (compare with p. 112).

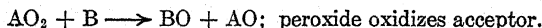
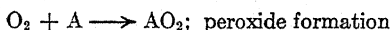
**Auto-oxidation.** Benzaldehyde and certain of its derivatives show a rather surprising behavior when exposed to atmospheric oxygen. They absorb oxygen fairly rapidly, forming an intermediate compound which is **benzoyl hydrogen peroxide**,  $\text{C}_6\text{H}_5-$

COOOH, which then oxidizes another molecule of benzaldehyde to benzoic acid. This process is called **auto-oxidation**:



Although auto-oxidation is a common reaction, only in the case of benzaldehyde has an intermediate peroxide been isolated; however, peroxide formation probably is a necessary step in all auto-oxidations. The reaction is auto-catalytic; at the beginning the reaction is very slow and gradually it increases to a maximum velocity. The induction period (the time before the reaction is noticeable) indicates that either a certain concentration of peroxide must be formed before the rate becomes appreciable or minute amounts of impurities present as inhibitors must be removed. Generally auto-oxidations are very sensitive to catalysts, either positive or negative. Those of the latter class probably react with the intermediate peroxide and thus destroy it. Among such negative catalysts, which are called **anti-oxidants**, are those polyhydroxy compounds and aminophenols which are readily dehydrogenated by very mild oxidizing agents (Chap. XXI). As little as .001 per cent of hydroquinone in benzaldehyde will prevent its auto-oxidation.

Quite frequently substances which are perfectly stable to oxygen are oxidized when added to a system capable of undergoing auto-oxidation. A general equation for an auto-oxidation may be written in which A is the substance which forms a peroxide  $\text{AO}_2$ , and B the substance which takes oxygen away from the peroxide (acceptor). The acceptor may be another molecule of A or another easily oxidized compound.

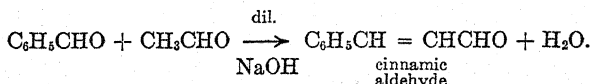


It often happens that the substance B (the acceptor) is not directly oxidized by atmospheric oxygen. The substance A (*e.g.*, benzaldehyde) thus serves to bring about the indirect oxidation of B. This is sometimes spoken of as a *coupled reaction*.

Compounds which may polymerize often do so when they undergo auto-oxidation. This probably means that the energy of the peroxide has been passed to a molecule of the substrate which is now in an active state ready either to combine with oxygen (auto-oxidation) or with another molecule (the first step in polymerization). We have pointed out previously that the discoloration and gum formation of cracked gasolines (p. 55) and the resinification of acrylic esters (p. 280) are catalyzed in some way by auto-oxidation. The addition of small amounts of inhibitors is essential in storing these substances since the anti-oxidants prevent auto-oxidation and subsequent polymerization.

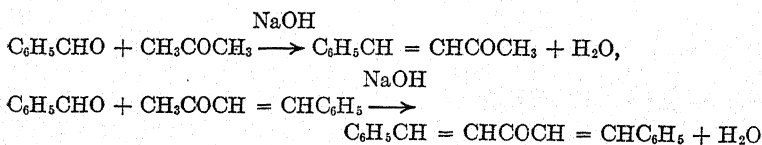
The drying of oil paints is another illustration of polymerization induced by auto-oxidation. In this case positive catalysts for the auto-oxidation process are often added.

**Side-Chain Compounds from Benzaldehyde.** Compounds which contain an aromatic nucleus and a reactive group separated by a chain of carbon atoms are often called side-chain compounds. Many such substances can be synthesized with the aid of benzaldehyde. Substances which have a hydrogen in the alpha position to a carbonyl group react with benzaldehyde with the formation of *unsaturated side-chain compounds*. The reaction is brought about by acids or by bases. If acetaldehyde is used, **cinnamic aldehyde** is the product:



This aldehyde is a liquid which boils at 252°. It is a constituent of oil of cinnamon and has a pleasant cinnamon odor.

A similar condensation takes place between an aromatic aldehyde and a ketone containing the grouping  $-\text{CH}_2\text{CO}-$ . For example, benzaldehyde will condense with acetone forming an unsaturated ketone. Depending on the proportion of the reactants, **benzalacetone**,  $\text{C}_6\text{H}_5\text{CH} = \text{CHCOCH}_3$ , or **dibenzalacetone**,  $(\text{C}_6\text{H}_5\text{CH} = \text{CH})_2\text{CO}$ , is formed:



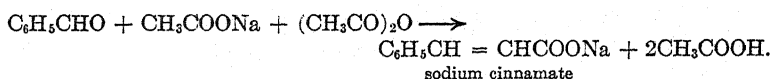
Dibenzalacetone is a yellow, crystalline solid (m.p. 112°) which is easily isolated and identified in small quantities. The formation of dibenzalacetone is, therefore, recommended as a procedure for identifying small quantities of acetone.

The condensation reactions just described are obviously analogous to similar reactions in the aliphatic series discussed in Chap. VI. There is little doubt that an aldol (p. 117) is an intermediate product in each case.

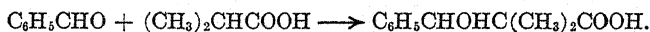
**Perkin Reaction.** Aromatic aldehydes will condense not only with aldehydes and ketones, but even with the sodium salts of aliphatic acids. This reaction is known as the Perkin<sup>1</sup> reaction, and is characteristic of aromatic aldehydes. As an example, we

<sup>1</sup> William Henry Perkin (1838-1907). Discoverer of the first coal tar dyestuff, mauve, which he prepared while studying the action of oxidizing agents on crude aniline.

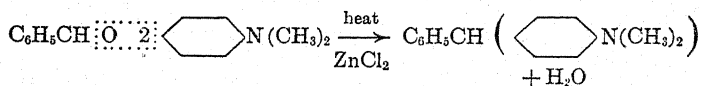
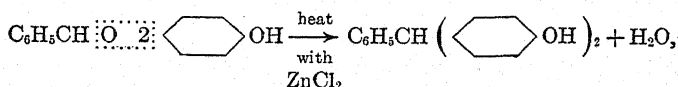
may cite the preparation of **cinnamic acid**,  $\text{C}_6\text{H}_5\text{CH} = \text{CHCOOH}$ . Acetic anhydride, sodium acetate, and benzaldehyde are heated together:



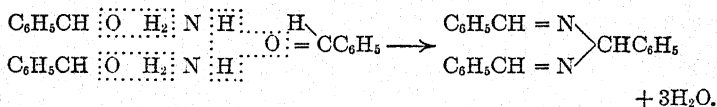
This reaction probably proceeds through an intermediate hydroxyl compound (analogous to an aldol),  $\text{C}_6\text{H}_5\text{CHOHCH}_2\text{COOH}$ , and like the other similar condensations, the hydrogen atoms on the *alpha* carbon atom are involved. Thus, if sodium propionate and propionic anhydride are used, the product is  $\text{C}_6\text{H}_5\text{CH} = \text{C}(\text{CH}_3)\text{COOH}$ . Isobutyric acid, which has only one hydrogen on the *alpha* carbon atom, reacts with benzaldehyde to give a hydroxy acid or its lactone:



**Certain Other Reactions of Benzaldehyde.** Benzaldehyde and many of its derivatives will condense with those aromatic compounds which have an easily replaceable hydrogen atom in the para position. For example, phenol and dimethylaniline react with benzaldehyde according to the following equations; the reaction is useful in the synthesis of certain types of dyes.

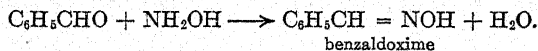


The reaction between ammonia and benzaldehyde is complicated. Three molecules of the aldehyde and two of ammonia condense in the following manner:

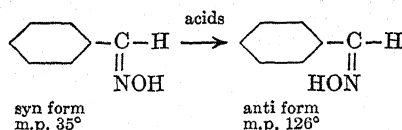


The product is known as **hydrobenzamide**; it is a colorless solid melting at  $110^\circ$ .

**Isomeric Benzaldoximes.** Two isomeric oximes can be prepared from benzaldehyde. The first product of the interaction of benzaldehyde and hydroxylamine is a crystalline solid which melts at  $35^\circ$ :

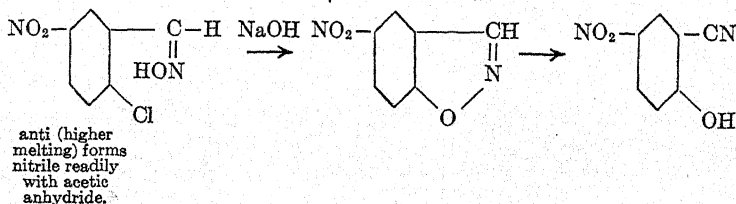


An isomeric substance melting at  $126^{\circ}$  is obtained by treating the low-melting oxime with hydrochloric acid. The two substances are geometrical isomers analogous to fumaric acid and maleic acid (p. 286). The double linkage between carbon and nitrogen prevents free rotation, and two stereoisomers are possible depending on whether or not the hydroxyl group and hydrogen atom are over each other. This type of isomerism has been observed in many cases with the oximes of aromatic aldehydes and ketones. Usually, in the aliphatic series only one form can be isolated. In the case of the isomeric aldoximes the terms *syn* and *anti* are used to designate the two forms.



The two isomers differ in some respects, especially in their behavior towards dehydrating agents. The higher melting isomer with acetic anhydride readily loses water to form benzonitrile,  $\text{C}_6\text{H}_5\text{CN}$ , whereas the dehydration of the lower melting isomer proceeds at a much slower rate. Because it seemed most likely that water would be eliminated from the compound in which the hydrogen atom and hydroxyl group are nearest together, the higher melting isomer was given the *syn* configuration. This, however, was later proved to be incorrect.

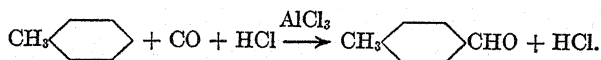
The manner in which the configurations of the isomers were determined is interesting. To settle this point a derivative of benzaldoxime, 2-chloro-5-nitrobenzaldoxime was used. The two geometrical isomers were treated with alkali. The higher melting isomer (again obtained from the lower by acid treatment) lost hydrogen chloride to form an unstable cyclic compound; the lower melting isomer under the same conditions did not lose hydrogen chloride. This proves that the higher melting compound had the *anti*-configuration (OH nearest the Cl of the ring).



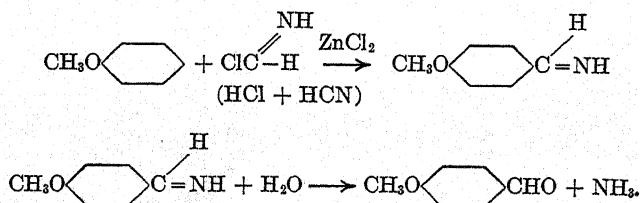
**General Methods of Preparing Aromatic Aldehydes.** In addition to the methods of preparing benzaldehyde mentioned at the beginning of this chapter, there are a few other general methods of importance.

Aromatic aldehydes can be prepared from the corresponding acids by distilling a mixture of the calcium salt with calcium formate (see p. 110). They may also be prepared by cautious oxidation of the corresponding alcohol. Both these methods are examples of the general methods of preparing aldehydes given in Chap. VI. The oxidation of an unsaturated compound is a very useful method of preparing certain aromatic aldehydes. Examples of this procedure will be given shortly (preparation of anisic aldehyde).

The aldehyde group may be directly introduced into the aromatic nucleus by two methods. The first may be illustrated by the preparation of *p*-methylbenzaldehyde (*p*-toluic aldehyde). It is really a modified Friedel-Crafts reaction (p. 333) since anhydrous aluminum chloride is the catalyst. A mixture of carbon monoxide and hydrochloric acid is employed which reacts as the equivalent of the unknown acid chloride of formic acid.



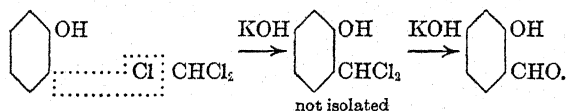
The second method of introducing the aldehyde group is employed with phenols and phenolic ethers. A mixture of hydrocyanic acid and hydrochloric acid is allowed to react with the phenol or phenolic ether; zinc chloride is usually employed as a catalyst or zinc cyanide and hydrochloric acid may be used which amounts to the same thing. The first product is the aldehyde imine which is readily hydrolyzed to the aldehyde. The mixture of acids probably forms some  $\text{HN}=\text{CHCl}$  which then reacts with the aromatic compound:



## HYDROXY ALDEHYDES

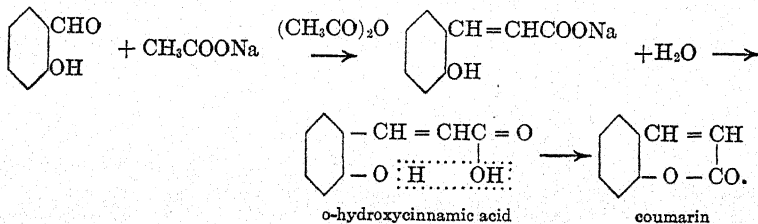
A number of hydroxy aldehydes and their ethers are important technically or are connected with interesting natural products. A few are used in the perfume industry.

**Salicyl Aldehyde,  $\text{HOC}_6\text{H}_4\text{CHO}$  (1, 2).** The ortho hydroxybenzaldehyde is called salicyl aldehyde. It occurs as a glucoside in a variety of plants. Salicyl aldehyde is prepared by a reaction which can be employed for introducing the aldehyde group into *phenols*, and is known as the **Reimer-Tiemann reaction**. This consists in heating the phenolic substance with chloroform and potassium hydroxide; a mixture of ortho and para compounds results in which the ortho predominates. The first product of the reaction is probably a dichloride (an hydroxy benzal chloride), which is then hydrolyzed to an aldehyde. This hypothetical intermediate is shown in the following equation:



Salicyl aldehyde is a colorless liquid boiling at  $196^\circ$  and solidifying at  $1^\circ$ . It has a pleasant odor.

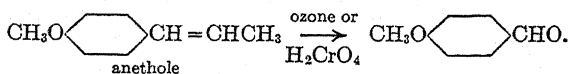
**Coumarin.** Salicyl aldehyde is manufactured as an intermediate in the synthesis of a substance of great importance in the perfume industry. This is coumarin, the inner lactone of **ortho hydroxycinnamic acid**. It is prepared by the Perkin reaction from salicyl aldehyde, sodium acetate, and acetic anhydride. The sodium salt of ortho hydroxycinnamic acid is first formed; on liberating the free acid by acidification, water is immediately lost and the lactone ring is formed:



Coumarin is a colorless, crystalline solid which melts at  $70^\circ$ . It is somewhat volatile, and has the odor of new-mown hay. Coumarin

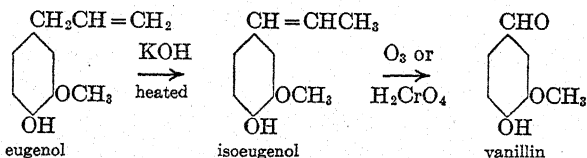
is widely distributed in nature usually as a glucoside; it occurs particularly in tonka beans from which it may be readily extracted. It is now prepared synthetically.

**Ethers of Hydroxy Aldehydes.** The methyl ether of para hydroxybenzaldehyde is known as **anisic aldehyde**,  $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$  (1, 4). It is present in the essential oil from the anise seed. It is prepared industrially by oxidizing an unsaturated compound, **anethole**, which is the chief constituent of anise oil:



Anisic aldehyde boils at  $248^\circ$  and solidifies at  $0^\circ$ . It has a penetrating fragrant odor, and is used in the perfume industry.

**Vanillin** is a monomethyl ether of a dihydroxybenzaldehyde. It is the principal odoriferous constituent of the vanilla bean. Like coumarin, it is a solid (m.p.  $81^\circ$ ) with a vanilla-like odor. Vanillin is prepared industrially for use as a flavoring material from guaiacol (p. 391) by introducing an aldehyde group (p. 407) or by oxidizing **isoeugenol**. Although the latter occurs in small quantities in essential oils (*e.g.*, nutmeg oil), it is prepared relatively cheaply by the rearrangement of **eugenol**, the chief constituent of **oil of cloves**. This rearrangement involves the shift of an ethylenic linkage:



Vanillin can be obtained from lignin (p. 436). The waste sulfite liquors of the pulp industry (p. 317), therefore, are a potential source of vanillin.

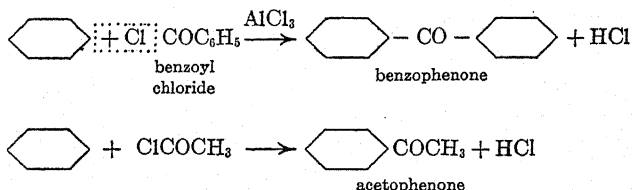
## AROMATIC KETONES

Aromatic ketones may be divided into three classes on the basis of the relationship of the aryl groups to the carbonyl group. The first class may be represented by **benzophenone**,  $\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$ ; the second by **acetophenone**,  $\text{C}_6\text{H}_5\text{COCH}_3$ ; and the third by **dibenzyl ketone**,  $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2\text{C}_6\text{H}_5$ . The members of all

three classes resemble the aliphatic ketones in most of their chemical properties. However, the immediate connection of an aryl group to a carbonyl group sets off the first two classes somewhat from the other ketones, and a few representatives of these will therefore be considered.

**Methods of Synthesis.** Aromatic ketones may be synthesized by most of the methods employed for the synthesis of aliphatic ketones (Chap. VI). Among these may be mentioned the destructive distillation of the calcium salts of the corresponding acids, the hydrolysis of a dihalide, and the oxidation of a secondary alcohol.

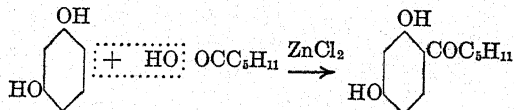
In addition to these general methods of synthesizing aliphatic and aromatic ketones, there is one specific method for preparing aromatic ketones which contain the grouping  $-\text{ArCO}-$ . This is the Friedel-Crafts reaction using an acid chloride, anhydrous aluminum chloride, and an aromatic hydrocarbon. It may be illustrated by the preparation of benzophenone (diphenyl ketone) and acetophenone (phenyl methyl ketone):



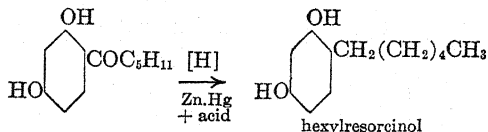
The aluminum chloride is a catalyst in this reaction as in the alkylation of aromatic hydrocarbons (p. 333). However, one mole of the catalyst must be employed because it usually combines with the product to form a loose addition compound, and thus is removed continuously from the reaction.

**Hydroxyketones.** The hydroxyl derivatives of benzophenone and acetophenone are prepared by somewhat different methods from those of the parent compounds or their other common derivatives.

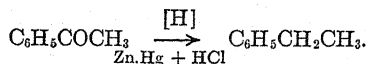
The hydroxyl compound, the corresponding acid, and zinc chloride are heated together. Water is eliminated and an acyl group directly introduced into the nucleus. For example, resorcinol and caproic acid,  $\text{C}_6\text{H}_4(\text{OH})_2$  and  $\text{C}_6\text{H}_{11}\text{COOH}$ , thus yield resorcylic amyl ketone:



This substance can be used for preparing hexylresorcinol (p. 390), since the oxygen of the carbonyl group is replaced by hydrogen by reduction with amalgamated zinc and acid:

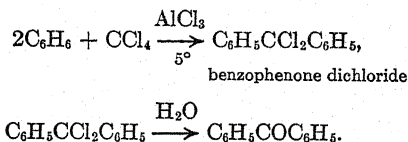


The reduction of the carbonyl group to the  $\text{CH}_2$  group by this method is applicable to aromatic ketones; for example, acetophenone yields ethyl benzene:



This reaction is often referred to as a **Clemmensen reduction**.

**Benzophenone.** Benzophenone may be prepared from benzoyl chloride and benzene by the Friedel-Crafts reaction, as we have just seen. A somewhat cheaper method is to use carbon tetrachloride, benzene, and aluminum chloride. If the amounts of reactants and the conditions are carefully controlled, the interaction of the carbon tetrachloride and the benzene can be stopped after only two of the four halogen atoms have been replaced. The dichloride is then hydrolyzed to the ketone:

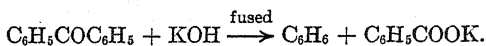


Benzophenone exists in two solid modifications. One melts at  $27^\circ$ , the other at  $48^\circ$ . These two substances must have the same molecular structure, since on melting they give the same liquid. The difference exists only in the solid state, in solution it disappears; it is due to a different arrangement of the molecules in the crystal. Different crystallographic modifications of this sort are known as **polymorphic forms** and the phenomenon is called **polymorphism**.

Benzophenone differs from most ketones in having no hydrogen atom on an alpha carbon atom. It will, therefore, not enter into condensation reactions which involve the removal of such an atom. In all other respects it is very similar in its reactions to acetone. It forms an oxime, is reduced to a secondary alcohol or

a pinacol, and reacts with the Grignard reagent; it does *not* add sodium bisulfite. It is very resistant to oxidation.

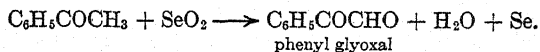
Benzophenone and other aromatic ketones are cleaved when fused with potassium hydroxide. This reaction is useful in determining the structure of such compounds.



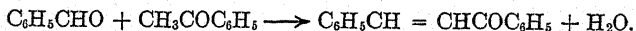
**Acetophenone.** This substance is the simplest example of a mixed aliphatic-aromatic ketone. Its preparation from acetyl chloride and benzene has been given above. In place of the acid chloride in this reaction the acid anhydride may be employed with somewhat better results. The aluminum chloride here definitely enters into the reaction since hydrogen chloride is evolved:



Acetophenone is a liquid boiling at 202° and solidifying at 20.5°. Except for the fact that it does not combine with sodium bisulfite, it has all the characteristic chemical properties of a methyl ketone (p. 121). For example, it is readily brominated, forms chloroform when treated with alkaline sodium hypochlorite, and condenses with aldehydes. With selenium dioxide it is smoothly oxidized to phenyl glyoxal:



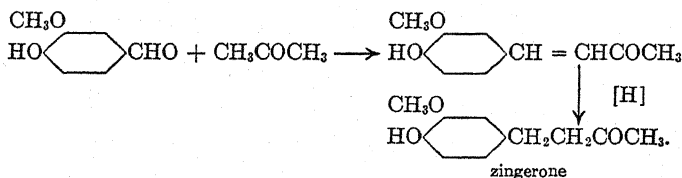
**Benzalacetophenone,  $\text{C}_6\text{H}_5\text{CH} = \text{CHCOC}_6\text{H}_5$ .** Benzaldehyde and acetophenone readily condense in the presence of dilute sodium hydroxide, forming an  $\alpha$ ,  $\beta$ -unsaturated ketone (p. 291), benzalacetophenone:



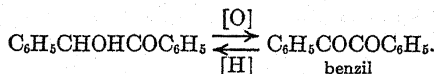
Benzalacetophenone is a yellow, crystalline solid which melts at 58°. Its reactions are similar to those of benzalacetone (p. 404), mesityl oxide, and other  $\alpha$ ,  $\beta$ -unsaturated ketones.

**Hydroxy Aromatic Ketones in Nature.** A number of hydroxy aromatic ketones and their ethers are found in nature. Only a few of these are of sufficient interest to warrant consideration here. Among the simplest are ortho and para hydroxyacetophenones,  $\text{HOC}_6\text{H}_4\text{COCH}_3$ , which occur as glucosides isolated from certain trees. Zingerone is one of the constituents

of ginger which imparts a biting taste to this material; it is 3-methoxy-4-hydroxybenzylacetone. The parent compound, **benzylacetone**,  $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCH}_3$ , may be prepared by the catalytic reduction of benzalacetone (p. 404). In the same way zingerone may be synthesized from vanillin:



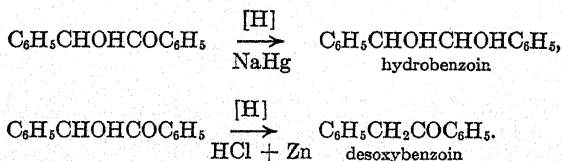
**Benzoin and Benzil.** The formation of benzoin from benzaldehyde has been discussed earlier in this chapter. Benzoin,  $\text{C}_6\text{H}_5\text{CHOHCOC}_6\text{H}_5$ , is a representative of the alpha hydroxy ketones. These substances are very easily oxidized to diketones. This oxidation or dehydrogenation may be brought about by complex cupric salts:



The diketone, **benzil**, is easily reduced back to benzoin. Benzoin is a colorless solid which melts at  $137^\circ$ ; benzil is a yellow, crystalline material which melts at  $95^\circ$ .

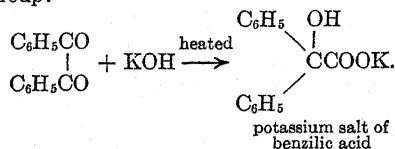
In spite of the ease of the oxidation and reduction, a careful study of the relation of benzil to benzoin has shown that it is different from the relation of quinone to hydroquinone (p. 387). The processes of oxidation and reduction are not rapid enough to make the system strictly reversible; they proceed at a measurable rate. An electrode immersed in a mixture of benzoin and benzil does *not* take on a definite potential (*cf.* the quinone-hydroquinone system, p. 387).

Reduction of benzoin with sodium amalgam yields **hydrobenzoin**, a glycol. The reduction of benzoin with zinc and hydrochloric acid causes the replacement of the hydroxyl group by hydrogen. The product is a phenyl benzyl ketone or **desoxybenzoin**:

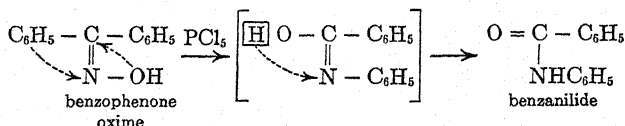


When fused with potassium hydroxide, benzil undergoes a remarkable rear-

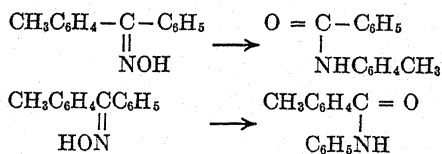
rearrangement known as the **benzilic acid transformation**. It involves the migration of a phenyl group:



**Structure of Ketones by Beckmann Rearrangement.** When benzophenone oxime is treated with certain reagents as phosphorus pentachloride or acetyl chloride a remarkable rearrangement occurs in which **benzanilide** (benzoyl aniline) is formed:



It should be noticed that the phenyl and hydroxyl groups trans (anti) to each other have changed places. We have purposely indicated this, since in cases of unsymmetrical ketone oximes where the configurations (syn or anti) have been established this trans shift is observed. If two isomeric ketoximes can be isolated, each form gives its own substituted amide by a trans shift. This is illustrated by the rearrangement of the isomeric oximes of phenyl *p*-tolyl ketone:



The Beckmann rearrangement offers a method of establishing the structure of a ketone, as the substituted anilide formed is readily hydrolyzed (p. 370) to a simple acid and amine. Thus, from benzophenone oxime, one can obtain benzoic acid,  $\text{C}_6\text{H}_5\text{COOH}$ , and aniline



#### QUESTIONS AND PROBLEMS

1. Write structural formulas for: benzyl phenyl ketone, vanillin, coumarin, benzoin, benzalacetophenone, salicyl aldehyde, benzil.
2. Compare and contrast the aliphatic and aromatic aldehydes.

3. Write equations illustrating: (a) methods of preparing aromatic aldehydes; (b) the use of the Friedel-Crafts reaction in the synthesis of ketones; (c) three condensation reactions of benzaldehyde.
4. Outline the steps in the industrial synthesis of the following: benzaldehyde, coumarin.
5. Compare the auto-oxidation of benzaldehyde and the dehydrogenation of isopropyl alcohol to acetone. Why are both reactions often spoken of as oxidations?
6. What would you predict to be formed if benzalacetophenone were allowed to react with phenyl magnesium bromide?
7. Predict what you would expect to happen when the following substances were allowed to interact (write equations): (a) benzaldehyde and ethyl magnesium bromide; (b) benzaldehyde and a mixture of nitric and sulfuric acids; (c) benzoin and phenylhydrazine; (d) anisic aldehyde, acetic anhydride, and the sodium salt of propionic acid; (e) acetophenone and an alkaline solution of sodium hypoiodite; (f) anisic aldehyde and a solution of potassium cyanide.
8. Name four aromatic aldehydes or ketones of industrial importance give their uses, and state how each is prepared.
9. Outline a process for preparing hexylresorcinol from benzene, malonic ester, and *n*-butyl alcohol;  $(\text{C}_6\text{H}_5)_3\text{CCOC}_6\text{H}_5$  from benzophenone.
10. Write equations for the following reactions: (a) benzal acetone + HBr; (b) benzalacetophenone + aluminum isopropylate.
11. Starting with vanillin, how would you synthesize zingerone, 3-methoxy-4-hydroxy-benzyl acetone?
12. Prepare  $\alpha$ -chloroacetophenone from benzene and acetic acid by two methods.
13. Outline the synthesis of vanillin from guaiacol.
14. Predict the products formed when phenyl ethyl ketone is allowed to react with: (a) selenium dioxide; (b) benzaldehyde and NaOH; (c) bromine; (d) amalgamated zinc and hydrochloric acid.
15. A compound A,  $\text{C}_{10}\text{H}_{12}\text{O}$ , was found to form an oxime. When the oxime was treated with phosphorus pentachloride and the resulting compound hydrolyzed with alkali, para toluidine and propionic acid were isolated. What is the structure of A?

## CHAPTER XXIII

### AROMATIC ACIDS

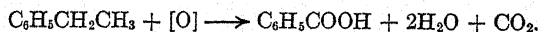
We shall consider in this chapter those acids in which a carboxyl group is directly joined to an aromatic nucleus or removed by one or more carbon atoms. On the whole, these acids differ less from the corresponding aliphatic compounds than any class of aromatic substances. For this reason, most of the chemical properties need be but briefly discussed. Three aromatic acids (benzoic, salicylic, and phthalic) are of industrial importance because they are used as intermediates in the preparation of dyes, drugs, and solvents. A number of aromatic acids and their derivatives occur in nature, and one large class of tannins is composed of condensation products of a trihydroxybenzoic acid.

#### COMPOUNDS WITH DIRECT UNION OF ARYL AND CARBOXYL GROUPS

**General Methods of Preparation.** The methods of preparing aromatic acids of the general formula,  $\text{ArCOOH}$ , may be illustrated by the preparation of benzoic acid,  $\text{C}_6\text{H}_5\text{COOH}$ . With certain exceptions, the same methods may be used for the preparation of a great variety of substituted benzoic acids and may, therefore, be considered as general methods. The preparation of aromatic acids by oxidation of the corresponding aldehyde (directly or indirectly by the Cannizzaro reaction) was considered in the last chapter and need not be repeated here.

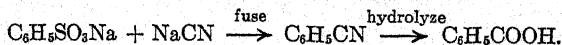
##### (1) *Transformation of a side chain to COOH:*

This can often be accomplished by direct oxidation if the molecule contains no other groups which may be sensitive to oxidation:



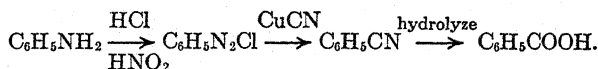
##### (2) *Replacement of $-\text{SO}_3\text{Na}$ by $-\text{COOH}$ :*

Fusion of a sodium sulfonate with sodium cyanide yields an aromatic nitrile, which may be then hydrolyzed to the acid:

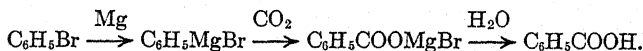


(3) *Replacement of  $-NH_2$  by  $-COOH$ :*

A primary amine is diazotized, converted to a nitrile (p. 379), which is hydrolyzed:

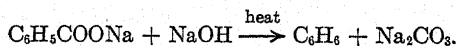
(4) *The use of a Grignard Compound:*

In this method an aryl halide is prepared, allowed to react with magnesium, and the organo-magnesium compound treated with carbon dioxide. Obviously the method is not applicable if the molecule can not be halogenated, or if it contains groups which react with the Grignard reagent (*e.g.*, the carbonyl group or groups with an active hydrogen):



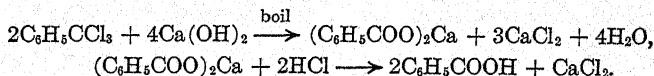
**General Characteristics of Aromatic Acids.** Although benzoic acid and its alkyl and halogen derivatives resemble the aliphatic acids in chemical properties, their physical properties are different. We proceed therefore somewhat differently in handling aromatic acids. For example, we prepare the free acid from the salt, not by distilling with sulfuric acid, but merely by acidifying a fairly concentrated solution of the soluble salt. Almost all the aromatic acids are insoluble in water, and at once precipitate when a water solution of their salts is treated with a strong acid.

Esters, acid chlorides, and acid anhydrides of aromatic acids can be prepared by the reactions used in aliphatic chemistry. On heating with sodium hydroxide, sodium benzoate forms benzene.



Some substituted benzoic acids lose carbon dioxide on gently warming the free acid. The preparation of pyrogallol is an illustration of this type of reaction (p. 391).

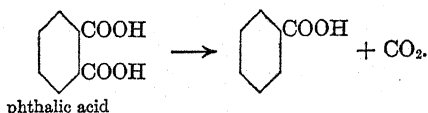
**Benzoic Acid.** This acid is a white, crystalline solid, melting at  $122^\circ$ , and is slightly soluble in water, easily sublimed, and volatile with steam. It occurs in the natural resin, gum benzoin, and in small amounts in cranberries. It is prepared on a large scale by hydrolysis of benzotrichloride,  $C_6H_5CCl_3$ , which is obtained by chlorinating toluene (p. 342).



The hydrolysis of the trichloride may first produce the ortho acid (p. 101),  $C_6H_5C(OH)_3$ , which then loses water and forms

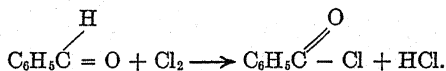
$C_6H_5C \begin{smallmatrix} O \\ // \end{smallmatrix} OH$ . Since benzoic acid is nearly insoluble in cold water, acidification of an aqueous solution of the salt produces a precipitate of the acid.

Benzoic acid is also manufactured by the catalytic decomposition of phthalic acid (p. 425) in the presence of steam. One carboxyl group is removed during this process:



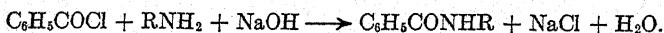
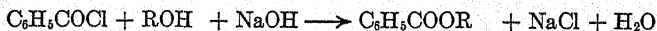
Toluene, benzyl chloride,  $(C_6H_5CH_2Cl)$  (p. 342), and a number of other substances can be oxidized to benzoic acid. The oxidation of toluene in the vapor phase by means of some inorganic oxide has been developed as an industrial method of preparation. Some benzoic acid has been prepared industrially by the oxidation of benzyl chloride with dilute nitric acid.

**Benzoyl Chloride.** The acid chloride of benzoic acid, benzoyl chloride,  $C_6H_5COCl$ , may be prepared in the usual way from benzoic acid and phosphorus pentachloride. It can also be prepared by a reaction which is peculiar to the aromatic series and which consists in chlorinating benzaldehyde:

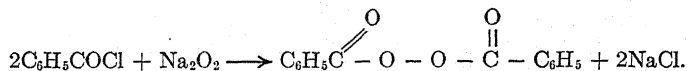


Benzoyl chloride is a liquid which solidifies at  $-1^\circ$  and boils at  $198^\circ$ . It has an acrid, irritating odor.

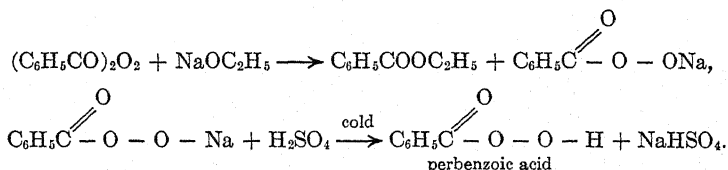
Benzoyl chloride is insoluble in water and reacts with it only slowly. In the presence of aqueous sodium hydroxide, it reacts with a variety of amino and hydroxyl compounds forming benzoyl derivatives. These derivatives are oftentimes solids of low solubility in water, and the reaction is used to prepare characteristic solid derivatives of alcohols and amines. The process is known as the Schotten-Baumann reaction; benzoyl chloride is shaken with an aqueous sodium hydroxide solution of the hydroxy or amino compound:



**Benzoyl Peroxide.** A very interesting compound can be readily prepared by the action of benzoyl chloride on sodium peroxide:



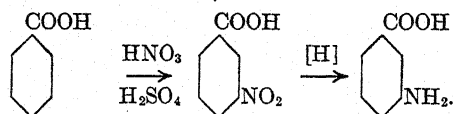
Benzoyl peroxide (also known as dibenzoyl peroxide) is a colorless, crystalline solid which melts at  $103^\circ$ . It is a derivative of hydrogen peroxide ( $\text{HOOH}$ ), in which both hydrogen atoms have been replaced by acyl groups. When it is treated with sodium ethylate one benzoyl group is eliminated. The product is the sodium salt of monobenzoyl hydrogen peroxide or **perbenzoic acid**:



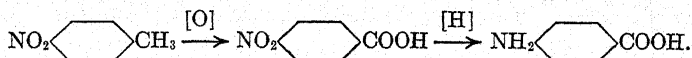
Unlike dibenzoyl peroxide, benzoyl hydrogen peroxide is unstable. It is a powerful oxidizing agent. It reacts with ethylene derivatives, adding one atom of oxygen to the double linkage forming an ethylene oxide derivative. It will be recalled that benzoyl hydrogen peroxide is the reactive intermediate in the auto-oxidation of benzaldehyde (p. 403).

**Derivatives of Benzoic Acid.** The carboxyl group directs a second substituent into the meta position. It is, therefore, an easy matter to prepare meta derivatives of benzoic acid or its esters by direct nitration, sulfonation, or halogenation. Substituted benzoic acids containing groups in the ortho or para position are usually synthesized by first preparing the corresponding ortho or para substituted toluene and then converting this to the corresponding acid by oxidation.

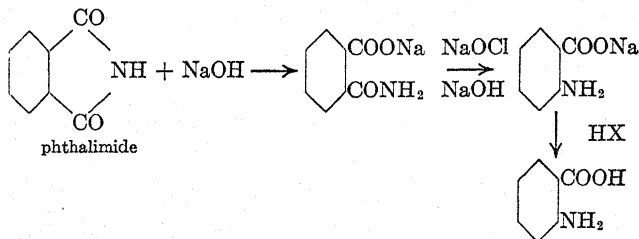
**Nitro- and Aminobenzoic Acids.** The nitration of benzoic acid yields meta nitrobenzoic acid from which by reduction the meta aminobenzoic acid is formed:



The para aminobenzoic acid can be prepared by the reduction of para nitrobenzoic acid which is formed by the oxidation of para nitrotoluene:



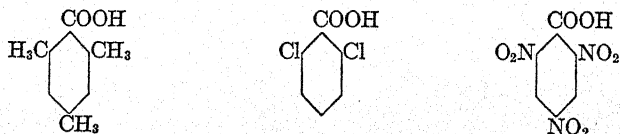
The ortho aminobenzoic acid is known as **anthranilic acid**. It is prepared by the action of alkaline sodium hypochlorite on phthalimide (the Hofmann reaction) (p. 151). The first step in this reaction is probably an hydrolysis by which the ring is opened and an amide is formed:



All three aminobenzoic acids are colorless, crystalline solids slightly soluble in water. They are amphoteric substances forming salts with acids or bases. The meta and ortho compounds are used in the preparation of certain dyes (the latter was formerly employed in the synthesis of indigo); para aminobenzoic acid in the form of its esters is used as a local anesthetic (see novocain, p. 536). The **methyl ester of anthranilic acid** occurs in certain essential oils, and is manufactured for use in the perfume industry. Its odor is reminiscent of grapes.

**Toluic Acids,  $\text{CH}_3\text{C}_6\text{H}_4\text{COOH}$ .** The three methyl benzoic acids can be made by the partial oxidation of the three isomeric xylenes. Dilute nitric acid is generally used as the oxidizing agent. They are all solids; the ortho melting at  $104^\circ$ , meta at  $110^\circ$ , and para at  $179^\circ$ .

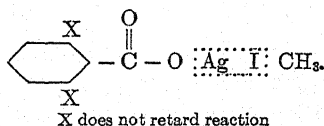
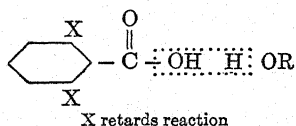
**Esterification of Ortho Substituted Acids.** Derivatives of benzoic acid which contain two substituents in the ortho position are peculiarly difficult to esterify by the direct method of heating with alcohol and acid. Such acids are, for example, the following (it is of no consequence whether or not the para position is also substituted):



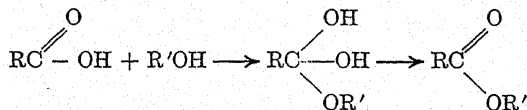
The esters may be readily prepared, however, by treating the

silver salt with methyl iodide (p. 95). When formed, the esters are hydrolyzed only very slowly.

These facts are similar to the behavior of tertiary acids and tertiary alcohols, which was mentioned in Chap. V (p. 99). It is interesting that in the case of the aromatic acids substitution in the ortho position (but *not* in the meta or para) has an effect equivalent to substitution in the alpha position in the aliphatic series. It is also significant that either a methyl group or a nitro group will suffice to retard the reaction, although these two groups are very different in many respects (*e.g.*, their effect on the basic strength of amines, p. 372). This suggests the idea that the effect may be due to the spatial bulk of the group rather than its influence through the ring on the carboxyl group. Such an explanation supposes that in the case of ortho substituted acids and highly substituted aliphatic acids, the reaction is retarded by spatial interference of the substituents. One may imagine that the approach of the alcohol group to within the sphere of influence of the carboxyl group may be hindered. Such an effect has been called "steric hindrance" by the advocates of this theory. The fact that the esters may be formed through the silver salt may be readily explained by this theory. In this case the reaction does not involve a group directly attached to the carbonyl group; it is one atom removed in space from the blocking groups and hence can proceed without interference:



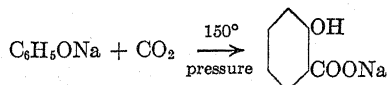
According to one theory of esterification, the first step in the process is the addition of a molecule of alcohol to the CO group of the carboxyl group. The resulting derivative of the ortho form then loses water forming the true ester:



If this is the real mechanism, the "steric hindrance" applies to the first step in the process. Indeed, it is found that the rate of addition reactions of aromatic aldehydes and ketones is tremendously decreased by ortho substitu-

tion. It will be noted that esterification through the silver salt could not involve an addition reaction of the carbonyl group.

**Salicylic Acid,  $C_6H_4(OH)COOH$  (1, 2).** This hydroxy acid is a solid melting at  $159^\circ$ ; it is more soluble in water than is benzoic acid. Sodium salicylate is prepared by a very remarkable reaction called the Kolbe <sup>1</sup> synthesis which is illustrated by the following equation:



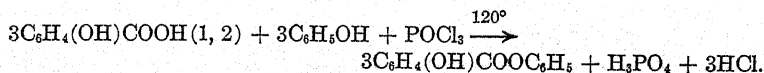
An intermediate phenol carbonate,  $C_6H_5OCO_2Na$ , is first formed; this then undergoes rearrangement.

**Sodium Benzoate and Salicylate as Preservatives.** Benzoic acid and salicylic acid in the form of their sodium salts are used as preservatives and very mild antiseptics. Enormous quantities of sodium benzoate are used each year in the preserving of fruits and vegetables, and in the manufacture of "ketchups." The legend "preserved with one tenth of one per cent of benzoate of soda" is probably familiar to all who have had occasion to scrutinize the labels on cans of preserved products. Sodium salicylate is used to a less extent. Sodium benzoate in the quantities used in preserving foods is generally believed to be non-injurious, although this has been a subject of some controversy and discussion. Both sodium benzoate and sodium salicylate are extensively used in the preparation of antiseptic medicinal preparations, such as tooth pastes and mouth washes.

#### MEDICINAL PRODUCTS FROM SALICYLIC ACID

The chief use of salicylic acid is in the preparation of three compounds of great medicinal importance: salol, aspirin, and methyl salicylate. Sodium salicylate itself has valuable medicinal properties, particularly in treating rheumatism. However, when taken through the mouth it is very largely absorbed in the stomach, and in many cases this leads to unpleasant symptoms. Chemists early endeavored in some way to modify the salicylic acid molecule so that these unpleasant effects would be overcome.

**Salol.** By esterifying salicylic acid with phenol the phenyl ester known as salol can be prepared:

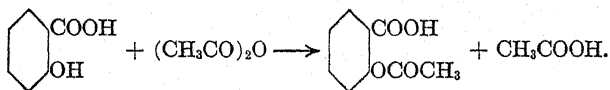


<sup>1</sup> Hermann Kolbe (1818-1884), Professor of Chemistry at the University of Leipzig.

It should be noted that, since salol is an ester of phenol, it can not be prepared by the usual esterification method; a special procedure involving phosphorus oxychloride and a relatively high temperature is employed.

Salol, being an ester, passes unchanged through the stomach, which is acid, but is hydrolyzed in the intestines, which are alkaline. Phenol and salicylic acid are there liberated and absorbed. Salol is, therefore, a powerful intestinal antiseptic and is widely used as such. It is also employed as a coating for medicinal pills whose content is effective only if liberated in the intestines. Such pills pass through the stomach intact but disintegrate in the intestine. Salol is a crystalline solid melting at  $42^{\circ}$ .

**Aspirin,  $C_6H_4(OCOCH_3)COOH$  (1, 2).** This is another salicylic acid derivative, one of the most familiar of all coal tar products. It is made by the acetylation of the phenolic group in salicylic acid:



Aspirin is a colorless solid melting at  $134^{\circ}$ ; it is insoluble in water. Its physiological action is probably due to the fact that it is hydrolyzed in the intestines, liberating salicylic acid which is there absorbed by the system. Aspirin has become a popular remedy for all complaints. Nearly 4,500,000 lbs. were manufactured in the United States in 1936; if this were all consumed in this country as five grain pills, it would correspond to an annual consumption of more than forty pills for each man, woman, and child!

**Methyl Salicylate,  $C_6H_4(OH)COOCH_3$ .** This ester occurs in certain plants and is the chief constituent of oil of wintergreen. It is a colorless liquid which boils at  $224^{\circ}$ , and has a pleasant wintergreen odor. It is made synthetically by esterifying salicylic acid in the usual manner with methyl alcohol. It is widely used in the flavoring industry and in the preparation of liniments and similar remedies for aches, sprains, and bruises. Methyl salicylate has the rather unusual property of penetrating the skin when rubbed on the surface. Probably hydrolysis takes place when the ester has penetrated, and the liberated salicylic acid has some physiological action which relieves the local pain.

## GALLIC ACID AND TANNINS

**Gallic Acid,  $C_6H_2(OH)_3COOH$  (3, 4, 5-trihydroxybenzoic acid).** Gallic acid is prepared by the hydrolysis of tannins. *It is not a coal tar product.* It is a solid soluble in water and crystallizes from the aqueous solution with a molecule of water of crystallization, which it loses on heating. When heated above  $200^\circ$ , it loses carbon dioxide and forms pyrogallol (p. 391).

**Tannins.** A group of substances of vegetable origin have long been known as the tannins. They are amorphous powders, soluble in hot water and also in ether. Their solutions have a very astringent taste and are colored dark blue-black or greenish by the addition of ferric salts. This latter fact has led to the extensive use of tannins in the manufacture of writing inks. Tannins react with **proteins** (Chap. XXXI); if the protein is soluble, as in the case of gelatine or white of egg, a voluminous precipitate is formed on adding a solution of a tannin. Insoluble proteins, such as the hide of animals, are changed by immersion in tannin solutions and the product is leather. The tanning of hides can also be brought about by using chromium compounds.

Tannins occur widely distributed. For tanning hides, it is common to use the bark of such trees as oak and hemlock. Formerly, the bark and hide were soaked together in vats; the tannin gradually dissolved and acted on the protein material. The more modern practice uses extracts of vegetable material rich in tannins. Solutions of these extracts are prepared and used in treating the hides.

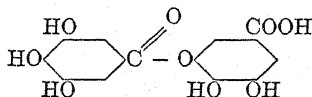
**Gallo-tannin.** The usual **tannic acid** of commerce is gallo-tannin. This is obtained principally from gallnuts, which are excrescences formed by the sting of insects on the branches of certain species of oak. Tannic acid is extracted from the powdered material with hot water. This material is used as a mordant in dyeing cotton cloth with basic dyes and also in the manufacture of inks. The commercial material may be further purified by extraction with ether or ethyl acetate; the tannin dissolves and is obtained by evaporation. Tannic acid is used in medicine as an astringent and for treatment of burns.

The study of carefully purified gallo-tannin has shown that it is a material of *high molecular weight*, which on hydrolysis with dilute sulfuric acid yields gallic acid and glucose. The relative

amounts of the products as well as the general behavior of the tannin itself point to the following formula:



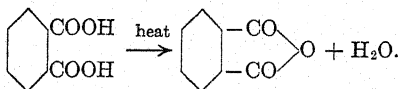
This is a penta-digalloyl-glucose. It is supposed that each hydroxyl group of glucose is esterified by **digallic acid**. A meta digallic acid has been synthesized which has the formula:



It will be noted that one hydroxyl group (in the meta position) of one molecule has formed an ester with the carboxyl group of the other molecule. A synthetic product obtained from glucose and the acid chloride of *m*-digallic acid resembles natural gallo-tannin in taste, solubility, optical activity, and the precipitation reactions. It is not identical with the natural material, however. Possibly the gallo-tannin itself contains para-digallic acid groups.

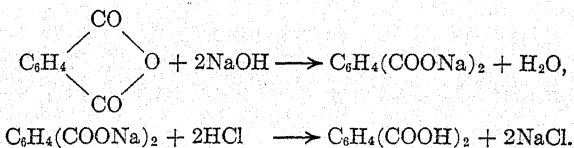
#### PHTHALIC ACID AND PHTHALIC ANHYDRIDE

The dibasic acid, **phthalic acid**,  $\text{C}_6\text{H}_4(\text{COOH})_2$  (1, 2), is the only aromatic dibasic acid of importance. It is a colorless solid almost insoluble in water; it melts at  $191^\circ$ . On heating just above its melting point, phthalic acid loses a molecule of water and forms **phthalic anhydride**, a cyclic anhydride:

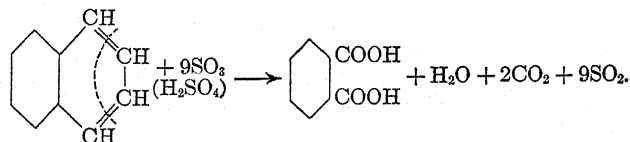


Like succinic anhydride (p. 202), this substance has a five-membered ring.

Phthalic anhydride melts at  $131^\circ$  and boils at  $285^\circ$ . It readily sublimates and is purified in this way. On treating with sodium hydroxide solution, the disodium salt of phthalic acid is formed, and on acidifying this solution phthalic acid precipitates:



**Preparation of Phthalic Anhydride.** Phthalic anhydride is of great importance as an intermediate in the dye and resin industries. During 1936 over 31 million pounds were produced in this country. It is prepared by oxidizing naphthalene,  $C_{10}H_8$ . For many years this was done by using fuming sulfuric acid as an oxidizing agent and mercury sulfate as a catalyst:



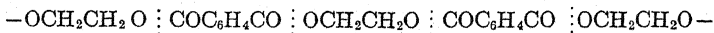
The enormous amount of sulfur dioxide evolved in the process was piped to a contact sulfuric acid plant. Here it was re-oxidized to sulfur trioxide, and used again to make more fuming sulfuric acid.

The discovery that mercury sulfate is an essential factor in the oxidation was the result of an accident. The action of fuming sulfuric acid on naphthalene was being studied; in one experiment a thermometer used in stirring the mixture was broken. Much to the chemist's surprise, excellent yields of phthalic acid were obtained. The action of mercury salts seems to be quite specific in this case, and only in their presence will fuming sulfuric acid oxidize naphthalene.

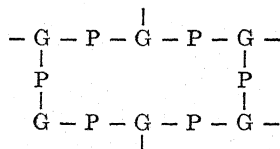
Since 1918 there has been developed a process for oxidizing naphthalene with air at about  $250^\circ$ . A mixture of the oxides of certain rare metals is the catalyst. If the conditions are not carefully controlled, either complete combustion takes place or the naphthalene comes through unchanged. This catalytic process has very largely replaced the older sulfuric acid oxidation. Since phthalic acid very easily loses water, the actual product of the oxidation of naphthalene is not the acid but the anhydride.

**Phthalic Acid Resins.** Next to the resins obtained from phenol and formaldehyde (p. 435), this class of resins is the most important. The resins of phthalic acid are made by heating the acid with polyhydroxy compounds in the presence of catalysts. During this process, esterification occurs between many molecules, giving substances of very high molecular weight. The resins of this class differ from those obtained from vinyl chloride (p. 276), acrylic esters, or from the polymers from isoprene (p. 76) in that they are not simple multiples of the monomer; during the building-up process water is continually split out. These macromolecules resemble cellulose in this respect (p. 318).

The polyhydroxy compounds used in preparing resins of phthalic acid are ethylene glycol and glycerol. With the former a long, straight chain substance is formed which is generally termed a **linear resin**. The structure may be illustrated as follows:

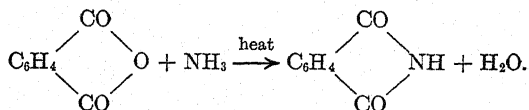


When glycerol is used poly-esterification may occur in such a way that two or more long chains are linked together because of the third hydroxyl group. These are known as **three-dimensional resins**. If we let P and G represent phthalic acid and glycerol respectively, a portion of this type of resin may be represented as follows:



The reactions which lead to resins are generally controlled to give products with suitable properties. The process is stopped at certain stages, and resins containing molecules of different sizes and linkages (linear or three dimensional) are obtained. Generally, the reaction is stopped before its final stage, the substance molded as desired, and then subjected to a final heat treatment. In the last stage, the smaller molecules unite producing a compound which is less soluble and higher melting than the intermediate product.

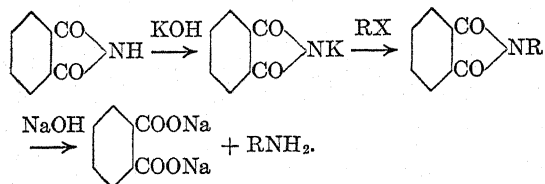
**Phthalimide.** A cyclic imide is formed by the action of ammonia on warm phthalic anhydride:



It will be recalled that amides with two acyl groups attached to the same nitrogen atom are known as imides (p. 205). Phthalimide is a crystalline solid which melts at 238°. Like the other amides and imides it has no basic properties, but it has weak acidic properties and forms a salt with potassium hydroxide.

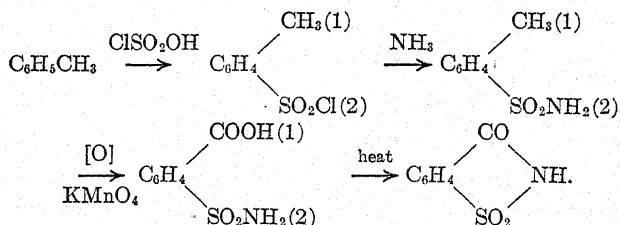
**Gabriel's Synthesis of Amines.** The potassium salt of phthalimide is used in the preparation of primary amines by Gabriel's synthesis. The potassium atom is replaced by an alkyl group when potassium phthalimide is heated with an alkyl halide. The substituted phthalimide may then be hydrolyzed to the sodium

salt of phthalic acid and a primary amine. The equations for the reactions are:



The advantage of this method of preparing primary amines is that the product is free from any secondary or tertiary amines.

**Saccharin.** An artificial sweetening agent seven hundred and fifty times as sweet as sugar is known as saccharin. Its sweet taste was discovered quite by accident in the course of purely scientific investigation. It is now manufactured for use as a sugar substitute for persons who are suffering from diabetes and can not eat carbohydrates. It is used in very dilute solution in which the sweet taste is most evident; in moderately concentrated solutions it has a bitter taste. Unlike a real sugar, saccharin is not digested and has no food value: it is thus a sugar substitute only as far as its sweetening power is concerned. During the sugar shortage caused by the World War it was widely used to make food and drink more palatable. Saccharin is the cyclic imide of ortho sulfobenzoic acid. It is in no way connected with the sugars. The reason for its sweet taste is a mystery. It is synthesized from toluene by the following steps:



In the first step in this synthesis chlorosulfonic acid ( $\text{ClSO}_3\text{H}$ ) is used as the sulfonating agent, and the product is the acid chloride of the ortho sulfonic acid, instead of the sulfonic acid itself which is formed if sulfuric acid is used. The hydrogen of the  $\text{>NH}$  group in saccharin can be replaced by sodium if the compound is treated with sodium hydroxide. This sodium salt

is much more soluble than the imide itself, and it is usually in this form that the substance is employed as a sugar substitute.

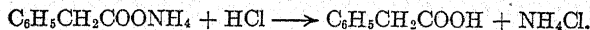
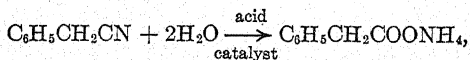
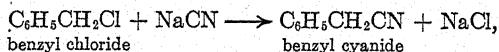
**Other Aromatic Polybasic Acids.** The isomers of phthalic acid are the meta compound, *isophthalic acid*,  $C_6H_4(COOH)_2$  (1, 3), and the para compound, *terephthalic acid*,  $C_6H_4(COOH)_2$  (1, 4). They are both colorless, crystalline solids. It is interesting that the meta compound will not form a cyclic anhydride although such a compound would contain a six-membered ring as in the case of glutaric anhydride (p. 203). The reason for this failure is evident if one constructs a model of isophthalic acid in which all six atoms of the nucleus are in a plane. It will be seen that the two carboxyl groups in the meta position can not come near enough together in space to allow the elimination of water. The chain-flexibility in glutaric acid permits the formation of the cyclic anhydride with six atoms in the ring; the rigidity of the planar benzene ring prevents the formation of a similar anhydride from isophthalic acid.

**Mellitic Acid**,  $C_6(COOH)_6$ , occurs as an aluminum salt called "honey-stone" in lignite and peat beds. Mellitic acid may be prepared by the oxidation of graphite or charcoal with nitric acid.

#### ACIDS WITH CARBOXYL GROUP IN THE SIDE CHAIN

A great number of saturated and unsaturated acids are known in which an aryl group is one or more carbon atoms removed from the carboxyl group. In general, these substances have the same chemical reactions as the corresponding aliphatic acids. Because of the heavy aryl group, they are usually solids and less volatile and less soluble than the aliphatic acids of the same length of chain.

**Phenylacetic Acid**,  $C_6H_5CH_2COOH$ . This is the simplest representative of a series of acids of the general formula  $Ar(CH_2)_nCOOH$ . It can be best prepared by the hydrolysis of the corresponding nitrile which is readily formed from benzyl chloride (p. 342) and sodium cyanide. The equations are:

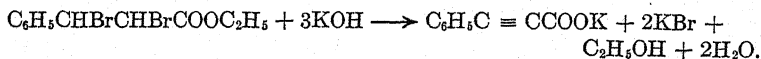
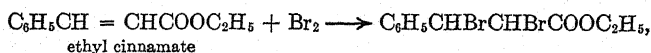


Phenylacetic acid melts at 76° and boils at 265°. It is only very sparingly soluble in water. It is used in small quantities in the form of its ethyl ester in the perfume industry.

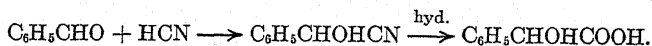
**Cinnamic Acid and Hydrocinnamic Acid.** The unsaturated acid, cinnamic acid,  $C_6H_5CH=CHCOOH$ , is readily prepared from benzaldehyde by the Perkin reaction as described in the last chapter. It occurs in certain essential oils and plant gums. Four modifications of cinnamic acid are known; they are all crystalline solids with different melting points. The common form of the acid melts at 133°; it is believed to be the *trans* form. The other modifications are different crystallographic forms of the *cis* acid; the difference in melting point is probably due to a different arrangement of the molecules in the crystal as in the case of the two modifications of benzophenone (p. 410).

Cinnamic acid has all the typical reactions of an  $\alpha$ ,  $\beta$ -unsaturated acid. On reduction with sodium amalgam or by catalytic hydrogenation, hydrocinnamic acid,  $C_6H_5CH_2CH_2COOH$ , is formed. This is also known as  $\beta$ -phenylpropionic acid. It melts at 48°.

**Phenylpropionic Acid,  $C_6H_5C \equiv CCOOH$ .** The ester of cinnamic acid readily adds a molecule of bromine forming a dibromide. On boiling this with alcoholic potassium hydroxide, an acid with an acetylenic linkage is formed:



**Mandelic Acid,  $C_6H_5CHOHCOOH$ .** The addition of hydrocyanic acid to benzaldehyde yields an hydroxy nitrile. This on hydrolysis forms an alpha hydroxy acid known as mandelic acid:

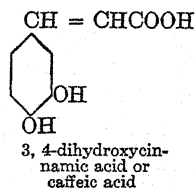
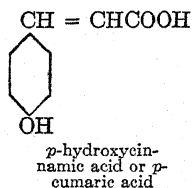
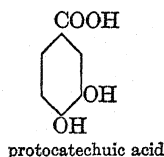


The hydroxy nitrile corresponding to mandelic acid occurs as the glucoside, amygdalin, present in bitter almonds (p. 401). Its enzymatic hydrolysis to benzaldehyde, hydrocyanic acid, and sugar has already been referred to.

Mandelic acid is a crystalline solid which melts at 118°. Its reactions are those typical of an alpha hydroxy acid (Chap. XI).

Its ammonium salt has found use in medicine as a urinary antiseptic.

**Occurrence of Aromatic Acids in Plants.** It is rather interesting to note that a few aromatic acids have been found widely distributed in the plant kingdom. These are: benzoic acid, salicylic acid (usually as the methyl ester), gallic acid, protocatechuic acid (and ester), *p*-hydroxycinnamic acid (cumaric acid) and 3, 4-dihydroxycinnamic acid (caffeic acid). The formulas for the acids in this list which have not been previously considered are given below.



In addition to these six substances but few other aromatic acids have been isolated from the plant world, and none found so widely distributed. The close relationship of these acids to each other is evident.

**Depsides.** A number of compounds are found in plants in which two molecules of hydroxy acids are united through an ester linkage. For example, digallic acid is such a compound. The name depside has been given to this class of substances. Di-depsides contain two such molecules thus joined, tri-depsides three, etc. Gallo-tannin is thus a complex di-depside, and probably other tannins contain the depside linkage.

A few simple di-depsides have been isolated from plants. One of these is derived from orsellinic acid,  $\text{C}_6\text{H}_2(\text{COOH})(\text{OH})_2\text{CH}_3$  (1, 2, 3, 5), have been isolated from lichens. This hydroxy acid, which contains a methyl group, seems to be a characteristic constituent of lichens, and is not found in other classes of plants.

### QUESTIONS AND PROBLEMS

1. Write structural formulas for the following: saccharin, gallic acid, aspirin, salol, oil of wintergreen, phenylacetic acid, mandelic acid, dibenzoyl peroxide.
2. Describe two commercial methods of preparing phthalic anhydride. What are the advantages of the new method?
3. Outline the steps in the synthesis of the following: *o*-chlorobenzoic acid (two methods) from *o*-toluidine; phenyl propionic acid from toluene; diethyl phthalate from coal tar; phenyl glyoxylic acid from benzene.

4. Write equations showing the reactions involved in the preparation of pyrogallol from tannin.

5. When acetomesitylene,  $\text{CH}_3\text{—}\langle\text{C}_6\text{H}_3\rangle\text{—COCH}_3$ , is treated with 1 mole

of methylmagnesium iodide, 1 mole of methane is liberated. On acidifying and working up the product, acetomesitylene is recovered. Explain these results.

6. How is salicylic acid manufactured? What important compounds are prepared from it? Write equations showing their preparation.

7. When acetophenone is treated with a mixture of sodium hydroxide and bromine, bromoform and benzoic acid are formed. When acetomesitylene

is treated in the same way  $\text{CH}_3\text{—}\langle\text{C}_6\text{H}_3\rangle\text{—COCH}_3$  is formed and no

cleavage occurs. How would you explain the difference?

8. Outline the various methods, using equations, by which primary amines may be prepared without contamination by secondary and tertiary amines.

9. Which of the following acids would form cyclic anhydrides on heating with a dehydrating agent:  $\text{CH}_3\text{CH}(\text{COOH})_2$ ,  $\text{C}_6\text{H}_4(\text{COOH})_2$  (1, 3),  $\text{CH}_2(\text{COOH})\text{CH}_2\text{CH}_2\text{COOH}$ ,  $\text{CH}_2(\text{COOH})\text{C}(\text{CH}_3)_2\text{COOH}$ ,  $\text{CH}_2(\text{COOH})(\text{CH}_2)_5\text{COOH}$ ?

10. What is meant by the term "steric hindrance"? Which of the following acids would you expect to be difficult to esterify with ethyl alcohol by the direct method:  $(\text{CH}_3)_3\text{CCH}_2\text{CH}_2\text{COOH}$ ;  $(\text{C}_2\text{H}_5)_2\text{C}(\text{CH}_3)\text{COOH}$ ; 2, 6-dibromobenzoic acid; 2, 4, 6-tribromophenylacetic acid, ortho nitrophthalic acid? Would an isopropyl ester be easier to prepare? Give the reasons for your answers.

11. Given a mixture of *n*-octyl alcohol, ethyl benzoate, propionic acid, and benzaldehyde; how would you separate these by chemical methods?

12. Write equations showing how benzoic acid may be prepared from: aniline, *p*-toluidine, sulfanilic acid, anthranilic acid, phthalic acid.

13. A substance A with the empirical formula  $\text{C}_8\text{H}_6\text{O}_2\text{Cl}_2$  is soluble in sodium bicarbonate solution from which it can be recovered on acidification. When boiled with alcoholic alkali, it may again be recovered unchanged when the solution is acidified. On vigorous oxidation, it yields a dibasic acid which loses water on heating. The dibasic acid is readily esterified by boiling with alcohol and sulfuric acid to give a diester. What is the structure of A?

14. Indicate how the following pairs of compounds may be differentiated chemically:  $\text{C}_6\text{H}_5\text{COCl}$  from  $\text{HOC}_6\text{H}_4\text{Cl}$ -1, 2;  $\text{C}_6\text{H}_5\text{CONH}_2$  from  $\text{C}_6\text{H}_5\text{—NHCOCH}_3$ ; *o*- $\text{C}_6\text{H}_4(\text{COOH})_2$  from *m*- $\text{C}_6\text{H}_4(\text{COOH})_2$ ; *o*- $\text{CH}_3\text{OC}_6\text{H}_4\text{COOH}$  from *o*- $\text{HOCH}_2\text{C}_6\text{H}_4\text{COOCH}_3$ .

15. How many products would you expect from the addition of bromine to ethyl cinnamate with the formation of the dibromide?

## CHAPTER XXIV

### AROMATIC CARBINOLS AND ARYL DERIVATIVES OF ALIPHATIC HYDROCARBONS

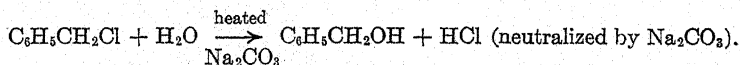
#### AROMATIC CARBINOLS

The simplest aromatic carbinol is the phenyl derivative of methyl alcohol,  $C_6H_5CH_2OH$ . This is known as **benzyl alcohol**. The homologs of this substance in which the phenyl group is one or more carbon atoms removed from the functional group are so like the aliphatic compounds that we shall not consider them. On the other hand, the secondary and tertiary carbinols in which

the aryl groups are directly connected to the  $-COH$  group, have certain peculiar and interesting reactions which are worthy of discussion. When the hydroxyl group itself is directly attached to an aryl group, we have a phenol. The distinction between phenols and aromatic carbinols is profound. These two classes of compounds have little in common: the aromatic carbinols are similar to the aliphatic carbinols; the phenols, on the other hand, are like the aliphatic enols.

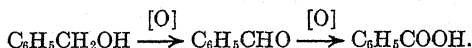
**Benzyl Alcohol,  $C_6H_5CH_2OH$ .** In all its reactions this compound is a typical primary alcohol. The physical properties, however, are different from the simple aliphatic alcohols. It is a colorless liquid which boils at  $206^\circ$ , possesses a faint, pleasant odor, and is only very slightly soluble in water.

Benzyl alcohol occurs in a variety of plants, usually as an ester. It is prepared for use in the perfume industry either from benzaldehyde by the Cannizzaro reaction (p. 402) or by the hydrolysis of benzyl chloride (p. 342).

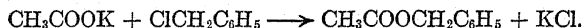


One of the differences between benzyl alcohol and the aliphatic primary alcohols is that it reacts with concentrated hydrochloric acid at *room temperature* to form benzyl chloride. The rates of

reactions involving the hydroxyl group are somewhat increased by the presence of the phenyl group. The other reactions of benzyl alcohol are those which are characteristic of a primary alcohol. For example, it can be oxidized to benzaldehyde and eventually to benzoic acid:

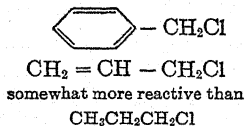
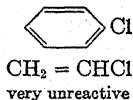


It is readily esterified by heating with an organic acid and a mineral acid as a catalyst. Benzyl acetate,  $\text{CH}_3\text{COOCH}_2\text{C}_6\text{H}_5$ , can be thus prepared. It is also formed by heating benzyl chloride with potassium acetate. It is a pleasant-smelling liquid used in the perfume industry.



**Benzyl Chloride.** Benzyl chloride,  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ , is always manufactured by the chlorination of boiling toluene (p. 342). Benzyl chloride is a liquid which boils at  $178^\circ$ ; it has a pungent odor and a powerful effect on the tear glands (lachrymatory action).

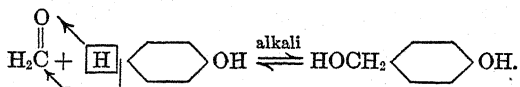
The halogen atom in benzyl chloride is reactive, and the typical reactions of alkyl halides are also characteristic of this substance. For example, potassium cyanide reacts with benzyl chloride, forming benzyl cyanide,  $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$  (p. 429), from which phenylacetic acid is prepared. Such metathetical reactions of benzyl chloride proceed more rapidly than in the case of the simple primary alkyl chlorides. It will be recalled that the same thing was true of allyl chloride ( $\text{CH}_2 = \text{CH} - \text{CH}_2\text{Cl}$ ) while vinyl chloride ( $\text{CH}_2 = \text{CHCl}$ ) was very unreactive (Chap. XVI). The phenyl group is thus similar to a vinyl group in its action;  $\text{C}_6\text{H}_5\text{Cl}$  is very unreactive, while  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$  is somewhat more reactive than an alkyl halide.



**Hydroxybenzyl Alcohols.** Ortho hydroxybenzyl alcohol,  $\text{HOC}_6\text{H}_4\text{CH}_2\text{OH}$  (1, 2), is known as *saligenin*. It occurs as the glucoside, *salicin*, in the bark of various species of trees. The

wide distribution in the plant world of the oxidation products of saligenin will be recalled. These are salicylic aldehyde (and its condensation product, coumarin) and salicylic acid. The chemical changes which occur in growing plants certainly include oxidation and reduction reactions; very probably all these ortho hydroxyl compounds have a common biochemical origin.

A mixture of ortho hydroxybenzyl alcohol and para hydroxybenzyl alcohol,  $\text{HOCH}_2\text{C}_6\text{H}_4\text{CH}_2\text{OH}$  (1, 4), is formed by the condensation of phenol and formaldehyde in the presence of alkali. This reaction is very similar to an aldol condensation (p. 117); the hydrogen in the ortho or para position is the equivalent in this case of the alpha hydrogen atom of a ketone or aldehyde. Like the aldol condensation, the reaction appears to be reversible:



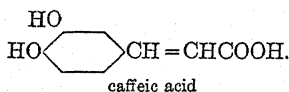
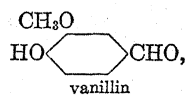
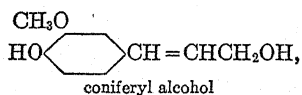
Both hydroxybenzyl alcohols on further heating with alkali form resins; this is the result of the formation of a large molecule by repeated condensation. A similar or perhaps identical product is formed as the result of the heating of phenol and formaldehyde with ammonia (Bakelite, p. 354).

**Cinnamic Alcohol**,  $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{OH}$ . This unsaturated alcohol is found in plants combined with cinnamic acid. The ester of cinnamic alcohol and cinnamic acid is the principal constituent of many balsams, of which the commonest is *storax*. As in the case of the ortho hydroxybenzyl alcohol derivatives, the occurrence in plants of cinnamic alcohol, cinnamic aldehyde, and cinnamic acid points to a ready biochemical interconversion of these compounds. The wide distribution of benzaldehyde (usually as a complex glucoside) is also of significance as the cinnamic compounds are transformed into this aldehyde by oxidation or formed from it by condensation (p. 404 and p. 405).

Cinnamic alcohol crystallizes in white needles which melt at  $35^\circ$  to a liquid which boils at  $257^\circ$ . It has the odor of hyacinth, and is used in the perfume industry. It may be prepared synthetically

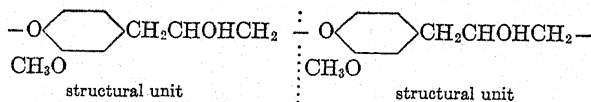
by the cautious reduction of cinnamic aldehyde (certain reducing agents, in particular aluminum isopropylate (p. 115), will reduce the aldehyde group to  $\text{CH}_2\text{OH}$  without attacking the ethylenic linkage). Cinnamic alcohol may be regarded as a phenyl derivative of allyl alcohol (p. 277). Its chemical properties are very similar to those of the parent compound and need not be enumerated again.

Coniferyl alcohol occurs as the glucoside, **coniferin**, in the sap of coniferous trees. It is related to vanillin just as cinnamic acid is related to benzaldehyde:



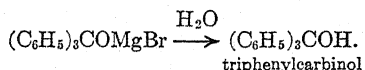
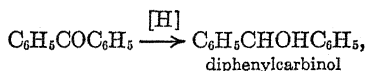
Caffeic acid (p. 431) is the corresponding acid but with the two phenolic groups free.

**Lignin.** It will be recalled that the cellulose aggregates in wood fiber are associated with an amorphous material of high molecular weight known as lignin (p. 317). Investigations of this amorphous material indicate that it is probably related to coniferyl alcohol and caffeic acid. Like other natural products of high molecular weight, there seems to be a regular recurrence of a definite structural unit. The probable fundamental unit of lignin is indicated in the following formula which has been tentatively suggested:

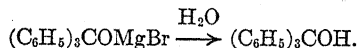
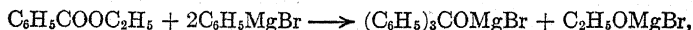


The units are joined by the ether linkage from one primary hydroxyl group to the phenolic group of the next molecule. Coniferyl alcohol could be formed from a molecule of the simple unit by dehydration; caffeic acid would result from oxidation and demethylation.

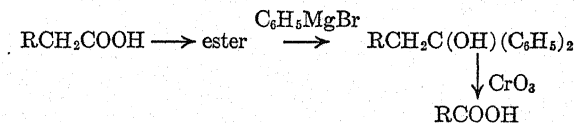
**Synthesis of Secondary and Tertiary Carbinols.** Secondary and tertiary alcohols containing aryl groups may be prepared by the same reactions as were employed in the aliphatic series. For example, benzophenone on reduction yields the secondary alcohol, diphenylcarbinol,  $\text{C}_6\text{H}_5\text{CHOHC}_6\text{H}_5$  (m.p.  $68^\circ$ ). The same ketone on treating with phenyl magnesium bromide forms triphenylcarbinol:



Another obvious method of preparing triphenylcarbinol is by the action of phenyl magnesium bromide on ethyl benzoate:



**Degradation of Carbon Chain.** In recent years the Grignard reagent prepared from bromobenzene has been employed in a series of reactions which enable one to degrade the carbon chain of an acid step by step. With complex substances this method has proved superior to that outlined on page 214. The principle of the two methods is not dissimilar. The ester of the acid in question is converted to a carbinol by the reaction given above. The carbinol on oxidation is cleaved to benzophenone and an acid with one less carbon than the original acid.



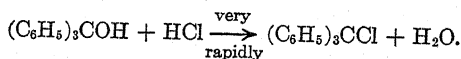
If a branched chain is present in the position next to the carbonyl group, a ketone is formed as the first oxidation product. However, with the strong oxidizing agent employed ( $\text{CrO}_3$ ), the ketone is usually not isolated but is oxidized with further cleavage to an acid. Thus, if a methyl group is located on the carbon atom adjacent to the carboxyl group, the result of this degradation is an acid with *two* less carbon atoms than the original acid:



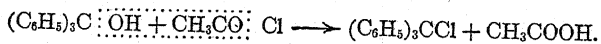
**Triphenylcarbinol.** This compound is a colorless solid which melts at 163°. It is the simplest representative of a large class of compounds of the general formula  $\text{Ar}_3\text{COH}$ . Many of such compounds have been synthesized because of their interesting and somewhat unusual chemical properties and their relation to the triphenylmethane dyes, which will be considered in a following chapter (Chap. XXX).

As would be expected from the fact that it is a tertiary alcohol, triphenylcarbinol is not oxidized. Since there is no hydrogen atom on a carbon atom adjacent to the functional group, it can not lose water and form an unsaturated hydrocarbon as most aliphatic alcohols so readily do.

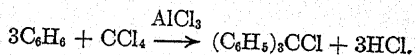
It will be remembered that tertiary butyl alcohol as a typical tertiary alcohol reacts very rapidly with hydrochloric acid; the same is true of triphenylcarbinol. The hydroxyl group is perhaps even more readily replaced than in the aliphatic tertiary alcohols, since the influence of the phenyl group (noted even in benzyl alcohol) is in this direction. When dry hydrogen chloride is passed into a solution of the carbinol, the corresponding chloride forms almost at once:



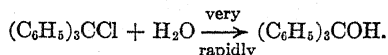
When the carbinol is treated with acetyl chloride, the hydroxyl group is replaced by chlorine instead of the acetate being formed. This may be considered as indicating that the hydroxyl group is very reactive, and the hydrogen very *unreactive*. The same reaction takes place with the few tertiary, aliphatic carbinols which have been studied.



**Triphenylchloromethane,  $(\text{C}_6\text{H}_5)_3\text{CCl}$ .** This chloride may be readily prepared from the corresponding carbinol as we have seen. It can also be conveniently synthesized by the Friedel-Crafts reaction from benzene and carbon tetrachloride; the temperature of the reaction mixture is in this case kept higher than when the dichloride is made from the same reactants (p. 411):

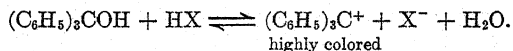


Triphenylchloromethane is a colorless solid which melts at 112°. The chlorine atom is replaced with extraordinary ease by a hydroxyl or methoxyl group when allowed to react with water or alcohol:



The peculiar compound formed by treating triphenylchloromethane with metals will be discussed later in this chapter.

**Basicity of Triarylcarbinols.** Triphenylcarbinol and its derivatives dissolve in concentrated mineral acids with the formation of highly colored salts. This phenomenon is known as **halochromism**. In the case of triphenylcarbinol, concentrated sulfuric acid is necessary in order to obtain the complete conversion to the halochromic salt. The para trimethoxy derivative,  $(\text{CH}_3\text{OC}_6\text{H}_4)_3\text{COH}$ , however, forms a halochromic salt even with aqueous hydrochloric acid. These halochromic salts may be isolated in many cases as highly colored crystalline solids; the perchlorates are particularly easily obtained. A study of these peculiar compounds has shown that they are salts formed from the carbinol and acid by loss of water. Since the positive charge is probably located on a carbon atom they are often called **carbonium salts**. Like almost all ionic reactions, their formation or hydrolysis is practically instantaneous.



It should be noted that the colorless triphenylchloromethane is *not* a halochromic salt. On dissolving it in some solvents, however, it probably dissociates at least in part, forming the colored ion,  $(\text{C}_6\text{H}_5)_3\text{C}^+$ , and the chloride ion.

It is extremely probable that the basicity of triphenylcarbinol is due to the fact that the resulting ion is an ionic hybrid being stabilized by a considerable amount of resonance energy. The resonating structures would be those in which the positive charge is located at the ortho or para positions of the aromatic nuclei, which are in the ortho or para quinoid state. Two such structures would be possible for each aryl group. The structure of one may

be written as  $(\text{C}_6\text{H}_5)_2\text{C} = \text{C}_6\text{H}_4 = \text{CH}^+$ . An ion  $\text{R}_3\text{C}^+$  in which all the groups are *alkyl* would not have the possibility of resonance.

It is significant that the trialkyl carbinols do not have basic properties.

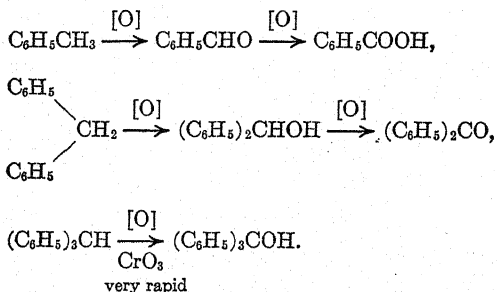
### ARYL DERIVATIVES OF ALIPHATIC HYDROCARBONS

**Aryl Derivatives of Methane.** Toluene is the simplest aryl derivative of methane. The phenyl derivatives of methane are listed below, together with their physical properties:

PHYSICAL PROPERTIES OF PHENYL DERIVATIVES OF METHANE

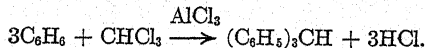
NAME	FORMULA	MELTING POINT	BOILING POINT
Toluene	$C_6H_5CH_3$	- 95°	111°
Diphenylmethane	$(C_6H_5)_2CH_2$	27°	262°
Triphenylmethane	$(C_6H_5)_3CH$	92°	359°
Tetraphenylmethane	$(C_6H_5)_4C$	285°	431°

With the exception of the tetraphenyl compound, they are all relatively easily oxidized. The final products are benzoic acid, benzophenone, and triphenylcarbinol, respectively:

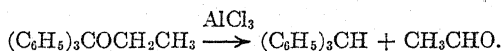


The ease with which the last two oxidations may be brought about illustrates the influence exerted by the accumulation of phenyl groups on the carbon atom.

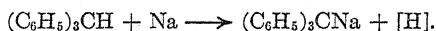
**Triphenylmethane.** This hydrocarbon may be synthesized from benzene and chloroform by the Friedel-Crafts reaction:



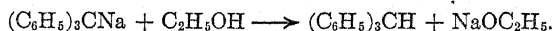
It may also be prepared by reducing triphenylchloromethane with zinc and an acid or from the ethyl ether of triphenylcarbinol by heating with aluminum chloride. In this reaction, the ethoxy group is oxidized to acetaldehyde:



**Acidic Properties of Triarylmethanes.** The triarylmethanes,  $Ar_3CH$ , of which triphenylmethane is an example, have very weak acidic properties. Triphenylmethyl sodium,  $(C_6H_5)_3CNa$ , may be formed, for example, by the action of metallic sodium in liquid ammonia solution on the hydrocarbon:



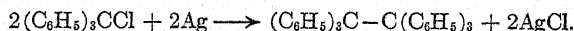
Such salts of the arylated methanes are highly colored, and soluble in organic solvents. They are undoubtedly somewhat dissociated into the ions  $(C_6H_5)_3C^-$  and  $Na^+$ . A similar salt of diphenylmethane may be prepared by indirect methods. The diaryl-methanes are much weaker acids than even the triaryl-methanes, however. The effect of the phenyl group on the methane carbon atom is thus cumulative. Triphenylmethane is a much weaker acid than even an aliphatic alcohol, and sodium triphenylmethyl reacts with alcohol as follows:



It is a matter of considerable interest that triphenylmethane has weakly acidic properties and triphenylcarbinol weakly basic properties. The presence of three phenyl groups appears to make possible the formation of either the ion  $(C_6H_5)_3C^+$  or  $(C_6H_5)_3C^-$ . The explanation of the stability of these ions as compared to similar ones containing only alkyl groups is that the presence of aryl groups permits of resonance.

**Hexaphenylethane.** Hexaphenylethane,  $(C_6H_5)_3C-C(C_6H_5)_3$ , has some very remarkable properties which are not at all characteristic of the parent hydrocarbon, ethane. The accumulation of phenyl groups, in this instance as in the case of triphenylcarbinol and triphenylmethane, has markedly altered the chemical reactions.

Hexaphenylethane was first prepared in 1900 by Gomberg.<sup>1</sup> The reaction he employed was similar to a Wurtz reaction:

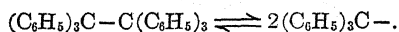


The resulting compound was a colorless, crystalline solid, as one would expect. But quite contrary to expectations *its solutions*

<sup>1</sup> Moses Gomberg (1866-). Professor of Chemistry at the University of Michigan.

were orange, and more surprising still they absorbed oxygen from the air with great rapidity. The oxygen absorption discharged the color of the solution, and a new, colorless, crystalline material separated. This compound on analysis proved to be a peroxide,  $(\text{C}_6\text{H}_5)_3\text{C}-\text{O}-\text{O}-\text{C}(\text{C}_6\text{H}_5)_3$ .

A careful study of hexaphenylethane and other hexarylethanes has shown that the peculiar behavior of these substances is due to the fact that in solution they are dissociated into *free radicals*. Thus, in a solution of hexaphenylethane there is always a mobile equilibrium between hexaphenylethane itself and triphenylmethyl,  $(\text{C}_6\text{H}_5)_3\text{C}-$ , the so-called free radical.



This free radical is colored and extraordinarily reactive. It combines with oxygen and halogens and is irreversibly polymerized in the presence of acids. The degree of dissociation increases with dilution according to the law of mass action. The equilibrium is shifted in favor of the free radical by raising the temperature. At  $5^\circ$  the dissociation of hexaphenylethane in a two per cent solution is not more than a few per cent. At  $80^\circ$ , however, the dissociation is 20 per cent, as shown by the molecular weight determination in freezing naphthalene.

**Other Free Radicals.** Some hexarylethanes have been synthesized which are practically completely dissociated in solution at room temperature. Probably the crystalline solid even in such cases, however, is the ethane and not the free radical. In solution, at least, a number of organic compounds exist in a form in which one of the carbon atoms is trivalent. These free radicals are exceptions to the general rule of the tetravalence of carbon, but their existence in no way affects the validity of the structural theory which was largely developed before their existence was discovered. The carbon to carbon linkage in ethane ( $\text{CH}_3 - \text{CH}_3$ ), butane ( $\text{C}_2\text{H}_5 - \text{C}_2\text{H}_5$ ), and diphenyl ( $\text{C}_6\text{H}_5 - \text{C}_6\text{H}_5$ ) is very different from that in hexaphenylethane. These simpler compounds do not dissociate into free radicals; if the corresponding free radicals are ever formed in the course of a reaction, they apparently firmly unite.

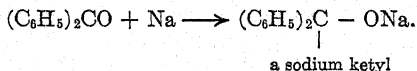
The difference between ethane and hexaphenylethane probably is connected both with the peculiar degree of unsaturation of aro-

matic groups and with the fact that they occupy more space than simple alkyl groups. Neither tetraphenylmethane, tetraphenylethane, nor pentaphenylethane at room temperature shows any of the peculiarities of hexaphenylethane. On the other hand, derivatives of ethane with only four aryl groups and two *branched* alkyl groups have been prepared which, like hexaphenylethane, are dissociated into free radicals.

The action of aromatic groups in promoting the dissociation is well explained by the assumption that the free radical is stabilized by resonance of the radical due to the possibility of the free bond shifting into the aromatic ring. The effect of the branched alkyl groups is probably due to their steric effect in weakening the C—C linkage.

For many years all attempts to prepare free methyl and free ethyl radicals were without success. The products were always the well-known saturated or unsaturated hydrocarbons. However, evidence has been obtained that free methyl and free ethyl groups are formed at high temperatures by the thermal decomposition of hydrocarbons or metallo-organic compounds. Thus the vapor of lead tetramethyl,  $\text{Pb}(\text{CH}_3)_4$ , when passed rapidly through a hot tube decomposes with the formation of some free methyl groups,  $\text{CH}_3\cdot$ . These very soon combine to form ethane, however, and their presence can only be detected by special methods. It is evidently quite out of the question to isolate free alkyl groups.

A group of peculiar compounds known as the *metallic ketyls* also contain a trivalent carbon atom. These may be prepared in solution by the action of metallic sodium or potassium on diaryl ketones.

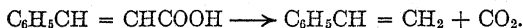


They are deep blue compounds which are very reactive towards oxygen or moisture. For this reason, like hexaphenylethane, they can only be prepared in the absence of oxygen.

**Odd Molecules.** Spurred on by Gomberg's discovery, a number of investigators have discovered compounds in which the elements have abnormal valence. Thus a number of free radicals containing divalent nitrogen have been prepared and a few which probably have a monovalent oxygen atom. All these substances

and those containing trivalent carbon atoms have been classed together as compounds whose molecules contain an uneven number of electrons and are therefore "odd molecules." These "odd molecules" are all colored in solution, have a great tendency to become "even," and thus react with a variety of reagents adding one atom or group to the unsaturated atom.

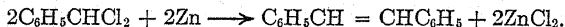
**Aryl Derivatives of Ethylene.** The simplest representative of this class of compounds is **styrene**,  $\text{C}_6\text{H}_5\text{CH} = \text{CH}_2$ . It is found in storax, where it is probably formed by decomposition of the cinnamic compounds which are present. It may be prepared by heating cinnamic acid:



Styrene is prepared industrially by several methods. In one of these ethyl benzene is dehydrogenated by heating in the gas phase at a high temperature in the presence of the oxides of certain metals.

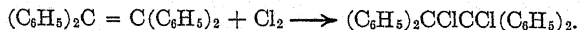
Styrene is a very reactive unsaturated hydrocarbon. It readily polymerizes to substances of high molecular weight when heated with various catalysts. These polymers find industrial use as resins.

Symmetrical diphenylethylene,  $\text{C}_6\text{H}_5\text{CH} = \text{CHC}_6\text{H}_5$ , is known as **stilbene**. It may be prepared as follows:



Both the *cis* and *trans* forms of stilbene are known. One is a solid (m.p.  $124^\circ$ ), the other an oil.

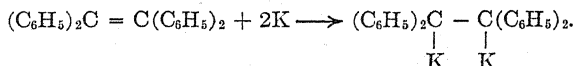
Tetraphenylethylene,  $(\text{C}_6\text{H}_5)_2\text{C} = \text{C}(\text{C}_6\text{H}_5)_2$ , is a substance in which the accumulation of phenyl groups around the ethylenic linkage has produced a marked effect. *It will not combine with bromine*, but does react with chlorine, forming a dichloride.



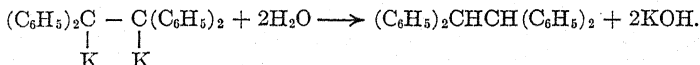
Other tetraaryl derivatives of ethylene have been prepared which will combine with neither bromine nor chlorine. These facts illustrate how a characteristic reaction of a particular linkage may disappear in a highly substituted derivative, particularly if the substituents are phenyl groups or unsaturated groups. Although tetraphenylethylene will not form a dibromide, it is reduced by hydrogen and a catalyst and combines with ozone. Therefore, towards

certain reagents the reactivity of the double linkage is unimpaired.

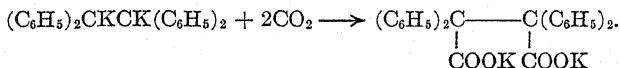
The double linkage in tetraphenylethylene differs from that in ethylene not only by its failure to combine with bromine, but by its reactivity towards a reagent which has no effect on the aliphatic hydrocarbons. This reagent is metallic potassium which combines with tetraphenylethylene forming a highly colored metallic compound.



When the addition compound is treated with bromine, the potassium atoms are removed and the unsaturated hydrocarbon regenerated. With water, the metallic atoms are replaced by hydrogen:



With carbon dioxide a substituted succinic acid is formed:



### QUESTIONS AND PROBLEMS

1. Write structural formulas for: diphenylcarbinol, saligenin, cinnamic alcohol, tetraphenylethylene, coniferyl alcohol, triphenylbromomethane, triphenylmethyl peroxide.

2. Outline steps in preparation from coal tar of: triphenylcarbinol, ethyl ester of cinnamic acid, diphenylmethane,  $\beta$ -phenyl-ethyl alcohol, benzyl benzoate, *p*-aminophenylacetic acid, *m*-nitro-cinnamic acid, benzylamine, diphenylcarbinol, and triphenylchloromethane.

3. State carefully in what respects hexaphenylethane differs from ethane or symmetrical diphenylethane,  $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$ .

4. Compare the chemical properties of phenol and benzyl alcohol; cinnamyl alcohol and phenyl ethyl alcohol; chlorobenzene and benzyl chloride. How do you account for the differences in properties?

5. Write balanced equations for the following reactions: (a)  $(\text{C}_6\text{H}_5)_3\text{COH} + \text{CH}_3\text{COCl}$ ; (b)  $(\text{C}_6\text{H}_5)_3\text{CCl} + \text{H}_2\text{O}$ ; (c)  $(\text{C}_6\text{H}_5)_2\text{CH}_2 + [\text{O}]$ ; (d)  $\text{C}_6\text{H}_5\text{CH} = \text{CHCOOH}$  (heated); (e)  $\text{C}_6\text{H}_5\text{COOAg} + \text{C}_6\text{H}_5\text{CH}_2\text{Br}$ .

6. Outline steps in the preparation of the following from benzene and an aliphatic compound: (a) cinnamyl alcohol; (b) diphenylethylcarbinol; (c) symmetrical diphenylethane; (d) coniferyl alcohol.

7. Discuss the behavior of the following compounds towards oxidizing agents: toluene, diphenylmethane, triphenylmethane, and tetraphenylmethane. Suggest some reason for the relative ease of oxidation of these compounds.

8. How are the ortho and para hydroxybenzyl alcohols prepared? What reaction in aliphatic chemistry is analogous to their mode of preparation?

9. A hydrocarbon,  $C_{17}H_{18}$ , on oxidation with  $CrO_3$  yields benzoic acid and an acid,  $C_{16}H_{12}O_2$ . The ester of the latter was treated with an excess of  $C_6H_5MgBr$  and the product oxidized; benzophenone and *p*-tolylacetic acid were the products. What is the structure of the hydrocarbon  $C_{17}H_{18}$ ?

10. Write formulas for all the resonating structures of: (a) the ion of sodium triphenylmethyl; (b) the ion of the halochromic salt of diphenyltolylcarbinol; (c) tri-(*p*-bromophenyl) methyl.

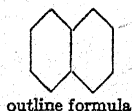
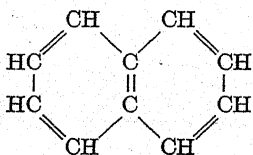
## CHAPTER XXV

### NAPHTHALENE, ANTHRACENE, AND PHENANTHRENE

Naphthalene, anthracene, and phenanthrene are present in the higher fractions which are obtained in the industrial refining of coal tar. The production of the first two substances on a large scale has resulted in their use in the manufacture of a great number of very important dyes. The three high-boiling, solid hydrocarbons, as we shall see, are aromatic compounds, but differ in certain important respects from benzene. Since there are two or more rings condensed together in the molecule of each of these substances, they are classified as condensed **polynuclear aromatic hydrocarbons**.

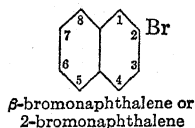
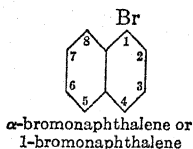
**Naphthalene.** Naphthalene,  $C_{10}H_8$ , is a white crystalline solid which melts at  $80^\circ$  and boils at  $218^\circ$ . It has an appreciable vapor pressure even at room temperature and readily sublimes on warming. Naphthalene has a pungent odor, and is commonly sold in flakes or balls for use as a protection against moths. It is prepared from coal tar as outlined on page 324. Since it occurs in relatively large amounts and is easily purified by distillation or sublimation, it is one of the cheap raw materials of the coal tar chemical industry (coal tar crudes). In 1935, over 47 million pounds of naphthalene were produced in the United States alone; however, to meet our demands, it was still necessary to import about the same quantity.

Naphthalene is very similar to benzene in many of its chemical properties. It can be nitrated, sulfonated, and halogenated; it yields *two isomeric monosubstitution products* and ten isomeric disubstitution products. It is represented by the following formula which adequately accounts for these isomers:



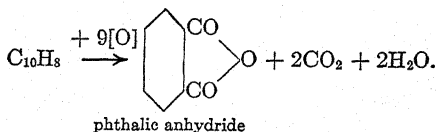
outline formula

The formula on the right is commonly employed. The monosubstitution products are divided into two classes, designated as alpha and beta:

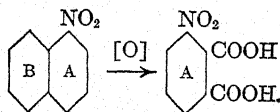


The position of substituents is also often indicated by numerals, as shown above. Clearly the 1, 4, 5, and 8 positions are the so-called alpha positions and 2, 3, 6, and 7 positions are the beta positions. All the alpha positions are equivalent to each other; the same is true of the beta positions. In other words, there are two and only two monosubstitution products.

**Proof of the Structure of Naphthalene.** As we have seen (p. 426), naphthalene is readily oxidized to phthalic anhydride and indeed is the industrial source of the anhydride and the corresponding acid:

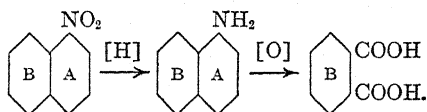


The fact that naphthalene yields phthalic acid on oxidation indicates the presence of one benzene ring in the molecule. A study of the oxidation of certain substituted naphthalenes establishes the presence of two condensed six-membered rings. The evidence is as follows: (1) by oxidizing alpha nitronaphthalene, nitrophthalic acid is produced:



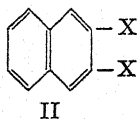
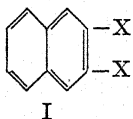
*This proves that the ring (marked A above) which holds the nitro group is a six-membered ring. (2) Alpha nitronaphthalene on*

reduction yields alpha aminonaphthalene and this on oxidation forms phthalic acid. In the first case the substituent (the nitro group) makes the ring difficult to oxidize; in the second, the amino group facilitates the oxidation.



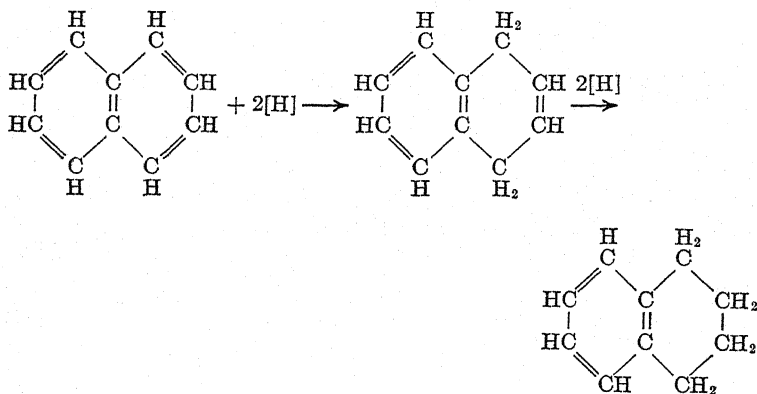
The fact that  $\alpha$ -aminonaphthalene yields an unsubstituted phthalic acid proves that the unsubstituted ring (marked B) in this compound and in  $\alpha$ -nitronaphthalene is also a six-membered ring. Therefore, it seems clear that naphthalene has two condensed six-membered rings. The carbon skeleton is thus established beyond question. The distribution of the hydrogen atoms about this skeleton is determined by the fact that there are two, and only two, monosubstitution products. Only a symmetrical distribution of the eight hydrogen atoms would lead to such a situation.

Like the benzene problem, the method of formulating the unsaturation of naphthalene has been much discussed. Just as in benzene one might at first sight expect two isomeric ortho disubstituted benzenes, so in naphthalene one might expect to find isomers of the type:

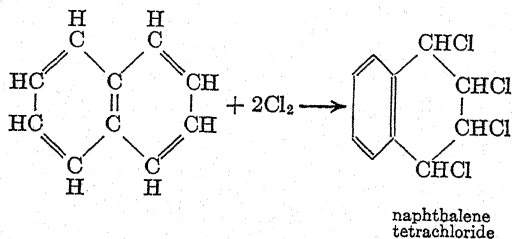


Such isomers have never been found. It will be noted that, as in the case of benzene derivatives, if such isomers existed they would be interconvertible without the shift of any atom or group. For most practical purposes, chemists usually employ the simple outline formula for naphthalene, though formulas essentially requiring an oscillation of bonds between types I and II above, centric formulas and a Thiele formula with a certain "free valence" at positions 1, 4, 5, and 8, and various electronic formulas find their advocates. We shall return to this problem after considering some reactions of naphthalene.

**Addition Reactions of Naphthalene.** Naphthalene has a more pronounced unsaturated character than benzene or its alkyl derivatives. Its oxidation to phthalic acid is one example of this. Naphthalene can be reduced by sodium and alcohol, a reagent which will not attack benzene. Four hydrogen atoms are taken up in pairs. The tetrahydronaphthalene now behaves like a dialkyl benzene and is very resistant to further hydrogenation:



Naphthalene combines with *four* chlorine atoms more easily than benzene forms a hexachloride (p. 328). The resulting naphthalene tetrachloride is clearly a benzene derivative just as is the tetrahydro compound mentioned in the preceding paragraph:

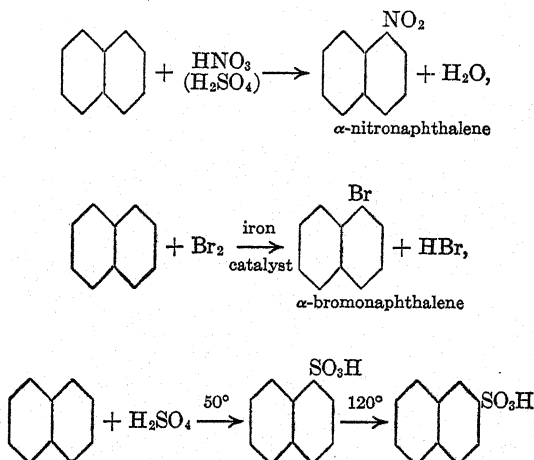


On heating naphthalene tetrachloride, hydrochloric acid is eliminated from the molecule and a mixture of chloronaphthalenes results. These are *substitution products* of naphthalene, of course. Such facts have led many chemists to believe that all substitution reactions in aromatic chemistry

(benzene derivatives included) are preceded by direct addition of the reagent to the double linkage of the aromatic compound. Careful studies of the rates of such reactions seem to indicate clearly, however, that this is not the mechanism of the usual course of aromatic substitution reactions.

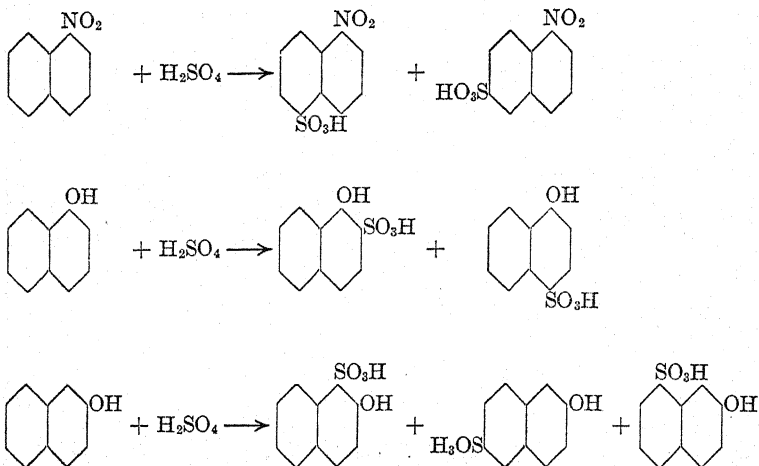
**Affinity of Naphthalene in Addition Reactions.** As the facts given above indicate, naphthalene differs from benzene in that the energy relationships are such that the addition reaction with one pair of hydrogen atoms goes to essential completion. Unlike benzene, the reaction is exothermic but like benzene the energy liberated is of a different order of magnitude from that evolved when an ordinary double bond is hydrogenated. The addition of  $H_2$  to naphthalene evolves only about 6–9 kg. cal. as compared to 28–30 for ethylene derivatives. In terms of resonance, we may say that the increase of stability due to the possibility of the existence of a number of different electronic formulas for naphthalene is great, but not so great as in the case of benzene (p. 329). This is undoubtedly due in large part to the fact that naphthalene is not as symmetrical a molecule as benzene.

**Substitution Reactions of Naphthalene Derivatives.** The typical aromatic reactions of benzene are also characteristic of naphthalene. Halogenation and nitration of naphthalene produce the alpha isomer. Sulfonation also goes in the same way, but at a higher temperature the alpha isomer rearranges to the beta:

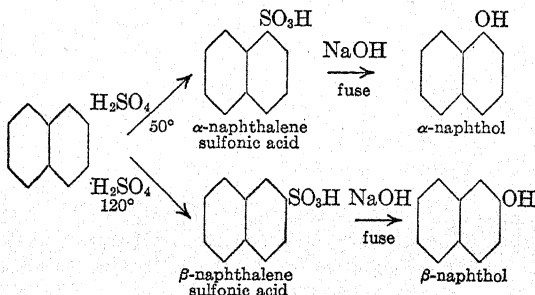


The introduction of a second substituent into the naphthalene ring follows the same general principles which we found to apply in the case of benzene. The nature of the group already present determines the position of the entering

group. As a general\* rule, meta-orienting groups ( $\text{NO}_2$ ,  $\text{SO}_3\text{H}$ ) cause the entering group to go into the other ring; this is in accord with the fact that the presence of such groups in a nucleus makes the introduction of a second substituent more difficult. Apparently the retarding influence of a meta-orienting group is confined to the ring to which the group is attached. The ortho and para orienting groups ( $\text{OH}$  and  $\text{NH}_2$ ) direct the incoming group to the 2 or 4 position (equivalent to the ortho and para positions in benzene). The same groups in the beta position favor the introduction of the second substituent in the alpha position or in the other ring. The following examples will serve as illustrations:

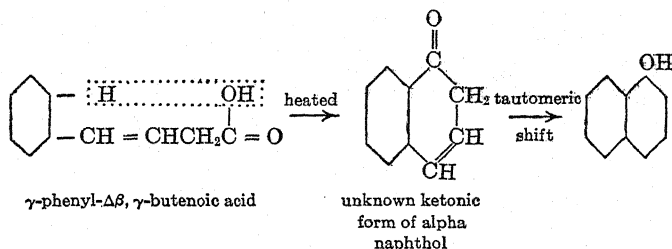


**The Naphthols.** The mono-hydroxy derivatives of naphthalene may be prepared from naphthalene by a process identical with that used for obtaining phenol from benzene. Thus, the two isomeric naphthols may be prepared as follows:



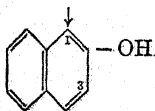
**Alpha naphthol**,  $C_{10}H_7OH$  ( $\alpha$ ), and **beta naphthol**,  $C_{10}H_7OH$  ( $\beta$ ), are solids melting at  $95^\circ$  and  $122^\circ$  and boiling at  $279^\circ$  and  $285^\circ$  respectively. They resemble phenol in their general reactions; they are weak acids, soluble in sodium hydroxide solution but not in sodium bicarbonate solution. They are prepared in large quantities for use in the manufacture of azo dyes (p. 548). They readily couple with diazonium salts;  $\alpha$ -naphthol couples in the 4 position,  $\beta$ -naphthol in the 1 position.

An interesting synthesis of a naphthol from a side-chain benzene derivative illustrates how readily the naphthalene structure is formed. By heating a  $\beta$ ,  $\gamma$ -unsaturated acid which has a phenyl group in the gamma position, water is eliminated; the first product of the reaction is probably the ketonic form of  $\alpha$ -naphthol, which immediately shifts to the enolic form.



The ketonic forms of the naphthols are unknown.

**Concerning the 1 and 3 Positions in Beta Substituted Naphthalenes.** At first sight it may seem remarkable that in the sulfonation of beta naphthol, no monosulfonated product is formed with a sulfonic acid group in position 3. By analogy with phenols one would expect that both ortho positions to the hydroxyl group in beta naphthol would be reactive. As a matter of fact, position 3 is very different from position 1. This is brought out most strikingly by a consideration of the coupling of naphthols with diazonium salts. Beta naphthol couples exclusively in the alpha position (1) and if this position

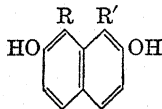


is occupied by some atom or group other than hydrogen, *no coupling occurs* even under the most drastic conditions. Though preferential coupling between two ortho positions in phenols is known, there is no analogy in the benzene series for this failure of the coupling reaction to proceed when an ortho position to OH is free. This and similar facts lead one school of chemists to

write the formula of beta naphthol with the linkages as indicated above. It is argued that if any of the isomers with the double linkage between atoms 2 and 3 were present, coupling should proceed in the 3 position as with phenols. Extrapolating from the hydroxy compound to the hydrocarbon such chemists prefer to write a naphthalene formula with all the double linkages shown and arranged as follows:



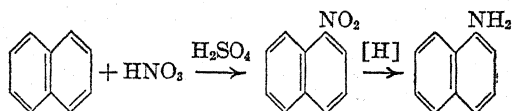
**A Useful Naphthalene Formula.** We have seen that there is no advantage to be gained from writing the double bonds into the formulas for benzene compounds. In the case of naphthalene, however, there is no doubt that as a matter of mere convenience there is much to be said for adopting such a practice. This is even more true of the still more complicated hydrocarbons with three rings. The formula above, as compared to an ambiguous outline formula or a centric formula or one with oscillating linkages, enables the reader to remember such facts as the failure of 2, 7-dihydroxy naphthalene to couple when both the 1 and 8 positions are occupied.



(It will not couple unless R or R' equals H.) Furthermore, this formula emphasizes the fact that while the affinity of naphthalene for hydrogen is much less than that of ethylene derivatives, it is much greater than that of benzene. In the reduction of naphthalene a pair of hydrogen atoms is added in either the 1, 2 or 1, 4 positions corresponding to 1, 2 and 1, 4 addition to conjugated open chain compounds (p. 73). On the other hand, it must be remembered that if we try to locate unsaturated linkages in aromatic compounds we are attempting to differentiate between isomeric possibilities of a totally different kind from those which confront us in non-aromatic chemistry (except for certain nitrogen compounds). The position of a double linkage in an open chain compound, for example, might be determined by locating the position of every alkyl group and hydrogen atom. An isomeric possibility would mean an alternative arrangement of atoms. Not so in the case of aromatic compounds: in writing double bonds in aromatic rings we are representing a different set of facts from those usually associated with establishing the position of unsaturation. We are representing a *mode of reaction rather than a configuration of atoms*.

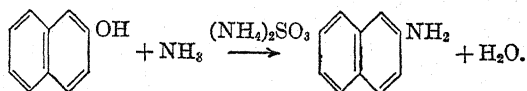
**The Naphthylamines.** The alpha naphthylamine is readily prepared from naphthalene by nitrating the hydrocarbon and then reducing the nitro compound. The process is thus exactly like

that used for the preparation of aniline from benzene:

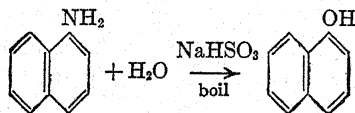


Alpha naphthylamine is a colorless solid which melts at 50° to a liquid which boils at 300°.

The beta isomer can not be readily prepared by a similar set of reactions, as the nitration of naphthalene yields only the alpha isomer. Fortunately, however, it is possible to replace the hydroxyl group by the amino group much more readily in the naphthalene series than in the case of benzene derivatives. This reaction is brought about by heating the naphthol with aqueous ammonia and ammonium sulfite. Since beta naphthol is easily prepared from naphthalene as we have just seen, beta naphthylamine is made from it by this reaction:



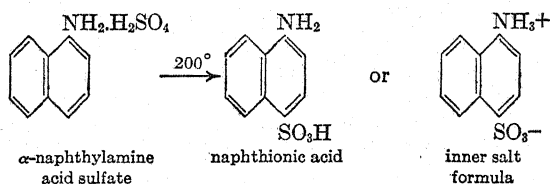
Beta naphthylamine melts at 112° and boils at 294°. Both amines are insoluble in water, but are soluble in aqueous solutions of mineral acids since they readily form soluble salts with acids. The amino group is very similar in its characteristics to the amino group of aniline. Thus, the naphthylamines can be diazotized to form diazonium salts. An amino group attached to a naphthalene nucleus may be replaced by an hydroxyl group by boiling a naphthylamine with an aqueous solution of sodium bisulfite.



**Sulfonated Naphthylamines and Naphthols.** A very important group of intermediates for the manufacture of azo dyes are the sulfonated naphthols and naphthylamines. The sulfonic acid

group is introduced into the molecule for the purpose of making the compounds *soluble in water*; this water-solubility survives even in the complicated azo dye molecule which is subsequently made from such a compound by a coupling reaction. The use of these compounds in the actual manufacture of dyes will become more evident when we consider the dyes themselves (Chap. XXX). At this point, we shall refer but briefly to a few of the more important of these intermediates.

**Naphthionic acid** is the naphthalene analog of sulfanilic acid (p. 367). Like the latter compound, it is prepared by baking the acid sulfate salt of the corresponding amine:

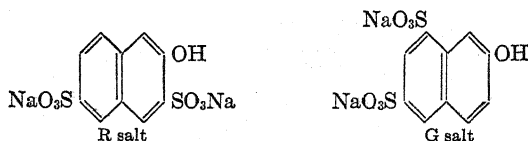


It very closely resembles sulfanilic acid and undoubtedly is an inner salt. It is practically insoluble in water but readily soluble in sodium carbonate solution due to the formation of the very soluble sodium salt. The aromatic amino sulfonic acids which contain the same number of amino and sulfonic acid groups in the molecule are nearly insoluble in water because they are really inner salts; they are isolated in this form. The introduction of another sulfonic acid group in the molecule makes the compound soluble in water like any other sulfonic acid, and such soluble sulfonic acids are usually isolated as sodium salts.

The **beta naphthol sulfonic acids** are prepared by sulfonating beta naphthol. (The orientation in this reaction has already been discussed.) Depending on the conditions, one, two, or three sulfonic acid groups are introduced. The sulfonated naphthols are very soluble in water and are usually isolated as the corresponding sodium salts by a "liming out" process (p. 348). The compounds which are thus prepared and sold are actually the sodium salts though they are frequently spoken of erroneously as though they were the free acid.

The sodium salt of beta naphthol-3, 6-disulfonic acid is known

as **R salt**; while *sodium beta naphthol-6, 8-disulfonate* is called **G salt**. These substances are used in the preparation of many

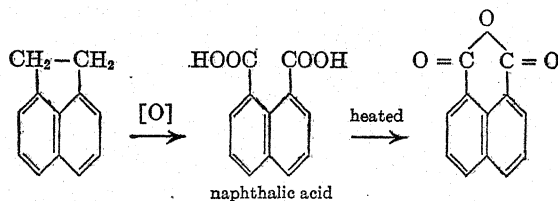


azo dyes. They readily couple in the 1 position with diazonium salts.

*1-naphthol-4-sulfonic acid* is known as Neville and Winther's acid (N. & W. acid), although it is actually prepared and used as the monosodium salt. **H acid** is 1-amino-8-naphthol-3:6-disulfonic acid which is actually employed as the monosodium salt (though the latter is often referred to as "H acid"). It is used in the manufacture of many important dyes.

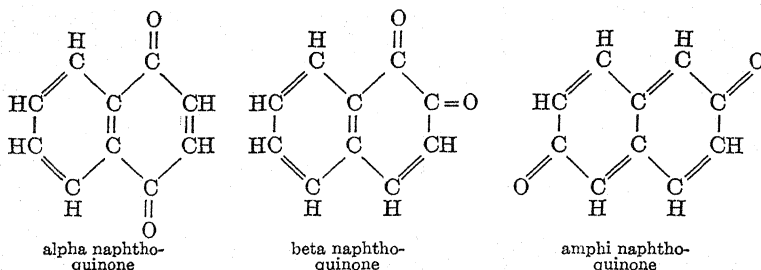
Another dye-stuff intermediate of importance is 2-hydroxynaphthalene-3-carboxylic acid. It is made by the Kolbe synthesis from beta naphthol. The carboxylic group enters the 1 position but on heating migrates to the 3 position.

**Naphthalic Acid.** This is an interesting dibasic acid derived from naphthalene in which two carboxyl groups are in the 1 and 8 positions. Two such groups are said to be in the *peri* position. The acid is formed by oxidizing acenaphthene, C<sub>12</sub>H<sub>10</sub>, a hydrocarbon occurring in small amounts in coal tar.



Naphthalic acid is similar to phthalic acid; on heating the free acid, water is eliminated and a cyclic anhydride is formed. Evidently groups in the 1, 8 positions in naphthalene have similar spatial relations to those in the 1, 2 positions in benzene. This is readily seen to be the case in a model in which both rings of the naphthalene nucleus are in the same plane.

**Naphthoquinones.** Three quinones related to naphthalene are known. They are known as alpha naphthoquinone, beta naphthoquinone, and amphi naphthoquinone.

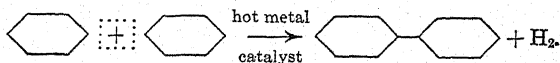


The relationship between the naphthalene quinones and the corresponding dihydroxy derivatives of naphthalene is exactly analogous to the relation between quinone and hydroquinone (p. 387). The naphthoquinones are prepared by oxidizing the corresponding dihydroxy compounds or corresponding aminohydroxy derivatives of naphthalene. Like the benzoquinones, the naphthoquinones are colored solids. The amphi and beta compounds are orange, the alpha quinone is yellow.

The alpha and beta naphthoquinones are to be regarded as related to 1, 4 and 1, 2 benzoquinone respectively, as naphthalene is related to benzene. The addition of another aromatic ring in this way has lowered the affinity of the quinone for hydrogen, and the corresponding dihydroxy compounds are thus oxidized by reagents which are not powerful enough to oxidize the corresponding benzene derivatives (*i.e.*, hydroquinone and pyrocatechol). The dehydrogenation of 2, 6-dihydroxynaphthalene to amphiquinone is more like the oxidation of hydroquinone, and in a sense this compound may be regarded as the true naphthalene analog of para benzoquinone.

### DIPHENYL

The hydrocarbon, diphenyl, has already been referred to a number of times. It can be prepared by the Wurtz-Fittig reaction from bromobenzene (p. 337), but is now prepared industrially merely by bringing benzene vapors in contact with a hot metal.



Diphenyl is a colorless crystalline solid which melts at 76° and boils at 254°; its high boiling point and great stability

on heating have made it useful where a high boiling liquid is required.

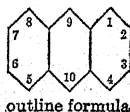
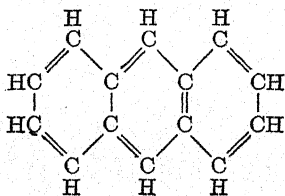
**Derivatives of Diphenyl.** Diphenyl is very similar to benzene in its reactions, as would be expected from its structure. Chloro, bromo, and nitro derivatives can be prepared by the usual procedures. The highly chlorinated diphenyls have been manufactured for use as plasticizers (p. 320).

One of the most important derivatives of diphenyl is benzi-dine (p. 376) but it will be recalled that this substance is not prepared from the hydrocarbon but from nitrobenzene by reduction.

#### ANTHRACENE AND ANTHRAQUINONE

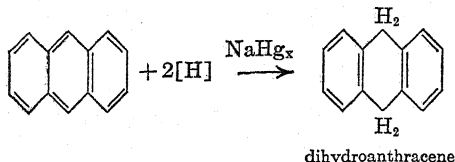
**Anthracene.** This hydrocarbon,  $C_{14}H_{10}$ , is present in the high boiling fractions of the coal-tar distillate. It is much more difficult to isolate and purify anthracene than the other "coal tar crudes." Indeed, in the United States at present a number of substances formerly prepared from anthracene are being synthesized from benzene derivatives. Therefore, the importance of the hydrocarbon itself as a raw material has diminished.

Anthracene is a colorless solid with a bluish fluorescence which is also weakly shown by solutions of the hydrocarbon. It melts at  $216^\circ$  and boils at  $342^\circ$ . In its chemical properties, it more nearly resembles an open-chain unsaturated hydrocarbon than does even naphthalene. For example, it readily combines with bromine or chlorine, is reduced to a dihydroanthracene by sodium amalgam, and is easily oxidized. At the same time, the typical substitution reactions of aromatic compounds can be brought about under certain conditions. The formula which best expresses the behavior of this interesting compound is the following, which is often written in outline as shown on the right:

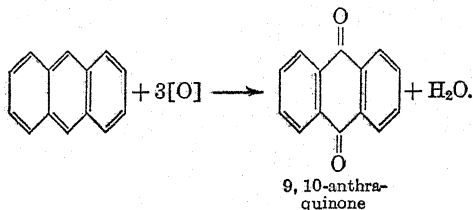


outline formula

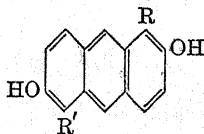
The method of numbering the ring is shown above. The two carbon atoms in the middle ring (9 and 10) are the points at which the anthracene molecule readily adds two atoms or groups. This may be represented by the reduction of anthracene to dihydroanthracene as follows:



The oxidation to 9, 10-anthraquinone is to be written as follows:



Bearing in mind the significance of double bonds in aromatic rings (p. 454) we have seen that in many cases it may be most convenient to write such linkages. The arrangement written above is preferred to all other possibilities (including various centric formulas) for a variety of reasons. It is clear that the left hand half of the formula as written above is essentially an ortho quinone (p. 389). It is therefore not surprising that the ends of this system (atoms 9 and 10) are the points of attachment of atoms or groups in addition reactions. The reduction of anthracene by one mole of hydrogen is thus analogous to the reduction of an ortho quinone. The affinity for one pair of hydrogen atoms in this position appears to be greater in the case of anthracene than even the affinity of naphthalene for hydrogen and to begin to approach that of ethylenic derivatives. (Estimated 15 kg. cal. of heat evolved as compared with 6 to 9 for naphthalene and -6 for benzene (*i.e.*, heat absorbed) and 28 to 30 for ethylene compounds.) This illustrates the fact that as far as the energy relations of addition reactions are concerned, there is no sharp line separating aromatic from aliphatic compounds. 2, 6-Dihydroxyanthracene will not couple with diazonium salts when the 1 and 5 positions are both blocked. If these positions are free, coupling in these places occur. These facts are expressed by the anthracene formula employed in this chapter.

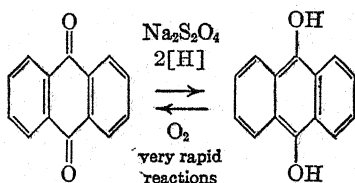


Will not couple unless R or R' is H.

**Anthraquinone.** The compound formed by the oxidation of anthracene is known as anthraquinone. It is very much more important than the hydrocarbon from which it may be prepared. A number of the most useful dyes are prepared from anthraquinone, and this compound is, therefore, one of the most important coal tar intermediates. Later we shall consider the actual dyes which are related to anthraquinone, and confine ourselves at this point to a consideration of the compound itself.

Anthraquinone is a yellow, crystalline solid which melts at  $284^{\circ}$ – $285^{\circ}$  and boils at  $382^{\circ}$ . It is not volatile with steam, and is difficultly soluble in most organic solvents. It will dissolve readily in warm, concentrated sulfuric acid, and may be recovered unchanged by diluting the solution with water. This fact is of use in the separation of anthraquinone from impurities, which are made water-soluble by such treatment.

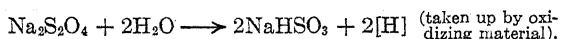
Anthraquinone is not reduced by agents such as sulfurous acid and hydrogen iodide which reduce benzoquinone. It is reduced rapidly, however, by zinc and alkali or sodium hydrosulfite,  $\text{Na}_2\text{S}_2\text{O}_4$ , with the formation of the corresponding dihydroxy derivative of anthracene (anthrahydroquinone). This compound dissolves in aqueous alkali with a characteristic red color; anthrahydroquinone is very rapidly oxidized to anthraquinone even by atmospheric oxygen:



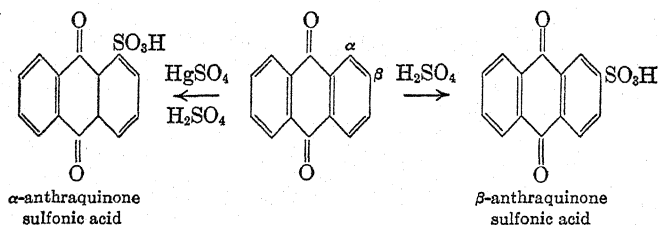
The relation between anthraquinone and its reduction product is exactly like that between quinone and hydroquinone (p. 387).

Sodium hydrosulfite (also known as sodium hyposulfite but not to be confused with hypo,  $\text{Na}_2\text{S}_2\text{O}_3$ ) is a powerful reducing agent as compared with sulfurous acid, hydrogen iodide, or stannous chloride, but is not so powerful as a metal since it will not liberate free hydrogen. It is much used in the

industry in the reduction of dyes (p. 558). When it acts as a reducing agent it is oxidized according to the following equation:

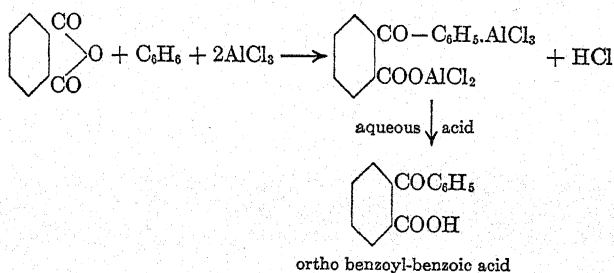


**Substitution Products of Anthraquinone.** Anthraquinone may be sulfonated by heating it with sulfuric acid (usually with the addition of some fuming sulfuric acid). Under ordinary conditions the sulfonic acid group enters the 2 position (known as the beta position); in the presence of mercury salts, the alpha sulfonic acid is produced.

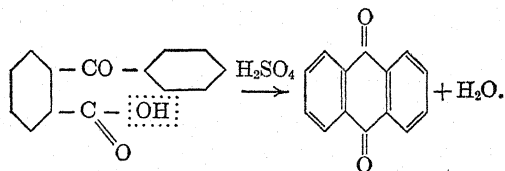


From these sulfonic acids (isolated in the usual way as sodium salts), the hydroxyl compounds can be obtained by fusion with sodium hydroxide. Certain of these hydroxyl compounds are important dyes and will be considered later. The amino derivatives of anthraquinone may be prepared by heating the hydroxy compounds with ammonia under pressure.

**The Synthesis of Anthraquinone.** Anthraquinone is now manufactured in the United States largely from phthalic anhydride and not from anthracene. This synthesis of anthraquinone is carried out in two steps: the first is a modified Friedel-Crafts reaction (p. 410), the second, a so-called condensation reaction in which the middle ring is closed:



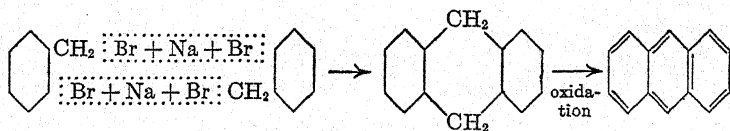
It will be noted that, like certain other examples of the Friedel-Crafts reaction which we have considered, an *acid anhydride* is here used instead of an acid chloride (p. 410). Two moles of aluminum chloride are employed and the product of the reaction is an aluminum salt which must be decomposed with acid to give the desired *ortho benzoyl-benzoic acid*. This substance when treated with concentrated sulfuric acid forms anthraquinone:



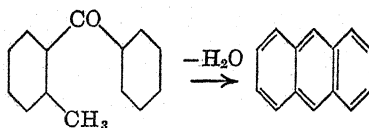
Substituted anthraquinones may be readily prepared by this same reaction using in place of benzene such substances as toluene or chlorobenzene, which yield beta methyl- and beta chloroanthraquinone, respectively, from the corresponding intermediates in which the substituent is in the para position.

**Structure of Anthraquinone and Anthracene.** The synthesis of anthraquinone from benzoyl-benzoic acid proves that there are three rings in the compound and that the two end rings are condensed benzene rings. The proof that the middle ring is also six-membered is provided by a number of facts which need not be considered here. The improbability of the closure of a meta or para ring in the synthesis from benzoyl-benzoic acid is evident from all that has been said in previous chapters about cyclic compounds.

The relation of anthraquinone to anthracene enables one to argue as to the structure of the carbon skeleton in one from that in the other. One of the earliest syntheses of anthracene was by the action of sodium on ortho bromobenzylbromide. Dihydroanthracene is probably the primary product but is oxidized to some extent to anthracene. This method of preparation afforded evidence of the correctness of the supposition that there were three condensed benzene rings in the molecule.

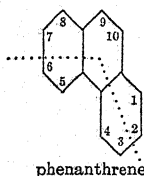


Another simple synthesis of anthracene is by means of the **Elbs reaction**. When ortho methyl benzophenone is heated, water is eliminated intramolecularly.



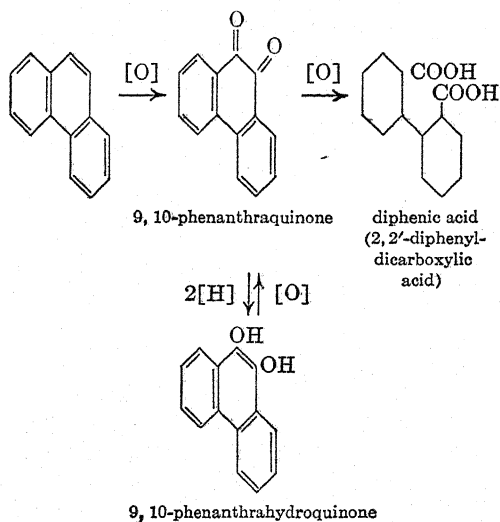
**Phenanthrene.** An isomer of anthracene is known as phenanthrene; it also occurs in coal tar and may be isolated from the higher fractions. Although it may be thus obtained without much difficulty, it is not usually separated because neither it nor its derivatives have been found to be of sufficient commercial value to warrant the expense of their manufacture. Unlike anthracene derivatives (or rather anthraquinone derivatives), the phenanthrene series of compounds seem to possess no characteristic which makes them more valuable industrially than the more accessible benzene and naphthalene compounds.

In phenanthrene three benzene rings are condensed together in what may be considered an angular manner as contrasted with the linear condensation in anthracene.

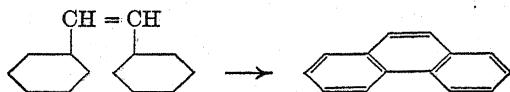


Phenanthrene, like anthracene, is a colorless solid with a slight fluorescence. It melts at 100° and boils at 340°. On oxidation, it is attacked at the 9, 10 position and yields 9, 10-phenanthraquinone. This substance is a typical quinone in regard to its relation to its reduction product, but it is reduced by less powerful reagents than those required to reduce the isomeric 9, 10-anthraquinone.

On further oxidation with chromic acid, phenanthraquinone is transformed into a derivative of diphenyl, known as **diphenic acid**:



Phenanthrene is formed when the vapors of stilbene (p. 444) are passed through a red-hot tube:

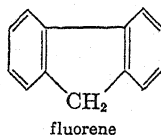
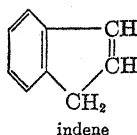


(At first sight the formula for phenanthrene written above seems to be different from that written on page 464, but the one becomes identical with the other by rotating the page.)

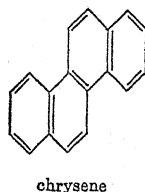
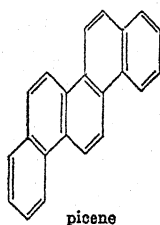
The distribution of the double linkages in the phenanthrene formulas written above corresponds to the modes of reaction of this hydrocarbon and its derivatives. The 9, 10 position is very nearly equivalent to an open chain double bond. Hydrogen can be added (one mole) in the usual manner; the heat evolved in this reaction is estimated to be about the same as in the case of anthracene. Bromine adds to form a dibromide, but the reaction is reversible and does not run to practical completion under the usual conditions.

**Other Condensed Aromatic Hydrocarbons.** A number of other polynuclear aromatic hydrocarbons occur in coal tar or may be prepared synthetically. Not only six-membered carbon rings, but also five-membered rings are found condensed with the benzene ring. Thus indene and fluorene

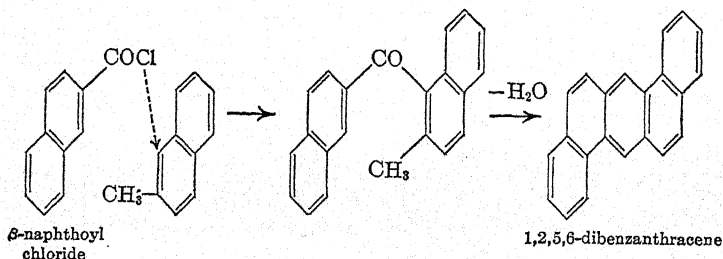
are analogous to naphthalene and anthracene except that a five-membered ring replaces a six-membered ring. They both occur in coal tar.



One of the hydrocarbons containing a very large number of condensed rings is picene,  $C_{22}H_{14}$ , which occurs in some varieties of coal tar. It melts at  $364^\circ$ . Chrysene,  $C_{18}H_{12}$ , is another highly condensed aromatic hydrocarbon which is found in coal tar. When obtained from coal tar, it forms beautiful golden-yellow crystals. The color, however, is due to an impurity which can be removed by repeated recrystallizations. Chrysene melts at  $255^\circ$ . We shall see later (p. 497) that chrysene is important in elucidating the structure of certain naturally occurring substances, since it is obtained from them as a degradation product.



**Carcinogenic Hydrocarbons.** It has been known for many years that the workers in coal tar refineries were susceptible to a skin cancer which came to be known as "tar cancer." A series of systematic investigations on coal tar revealed that certain aromatic, condensed, polynuclear hydrocarbons are responsible for this disease. One of the most active **carcinogenic** (cancer producing) compounds is 1, 2, 5, 6-dibenzanthracene. It can be synthesized by a Friedel-Crafts reaction between  $\beta$ -naphthoyl chloride and  $\beta$ -methyl naphthalene, followed by the application of the Elbs reaction.



An inspection of the structure of 1, 2, 5, 6-dibenzanthracene shows it is related to both anthracene and phenanthrene.

**Polynuclear Aromatic Compounds in Nature.** Although the chief interest and importance of naphthalene and anthracene derivatives centers around the coal tar dye industry, it would be a great mistake to believe that coal tar is the only source of these substances. Naphthalene, anthracene and phenanthrene derivatives (or substances closely allied to them, as for example the corresponding quinones) have been found in the vegetable kingdom. The occurrence of such substances, however, appears to be much rarer than the benzene derivatives, though this may be in part only a reflection of the greater difficulty of isolating such substances from the complex mixtures found in nature.

No simple naphthalene derivatives (such as the naphthols, for example) have been found in nature. Trihydroxynaphthalenes and derivatives of alpha naphthoquinone occur in certain very restricted classes of plants.

Derivatives of anthraquinone are quite widely distributed, though their occurrence is certainly much more specialized and localized than is the case of benzene derivatives. Alizarin and certain other hydroxy anthraquinones used as dyes will be discussed in the next chapter. Hydroxyl derivatives of a methyl-anthraquinone occur as glucosides in a number of plants. Plant extracts containing such materials are known under the general name of **emodine**, and are used as drugs chiefly because of their laxative and purgative action. **Chrysophanic acid**, 1, 8-dihydroxy-3-methyl-9, 10-anthraquinone, may be cited as an illustration of the substances occurring in such drugs.

We shall see in Chap. XXVII that a large group of substances which occur in nature contains the *hydrogenated* phenanthrene nucleus.

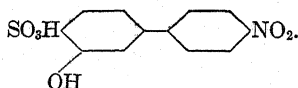
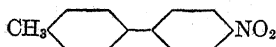
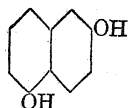
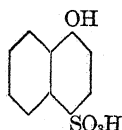
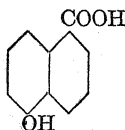
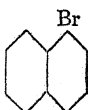
### QUESTIONS AND PROBLEMS

1. Write structural formulas for the following: R salt, 1-naphthol-4-sulfonic acid, naphthionic acid, indene, 9, 10-phenanthraquinone, 9, 10-anthrahydroquinone, 1-chloro-4-bromoanthracene, 2-hydroxy-naphthalene-3-carboxylic acid, beta naphthoquinone, naphthalene tetrachloride, decalin.

2. Discuss the structure of naphthalene, including a proof of the carbon skeleton and a consideration of the disposition of the double bonds.

3. Write the formulas for the different resonating structures of naphthalene and phenanthrene. Would you expect the naphthyl group to be approximately equivalent to the phenyl group in its effect on the dissociation of hexa-arylethanes? The diphenyl group? The benzyl group? Explain.

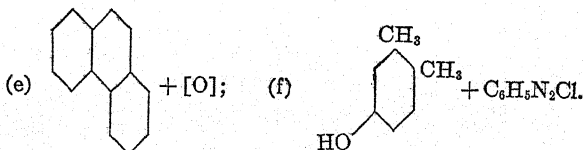
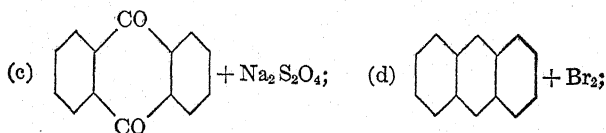
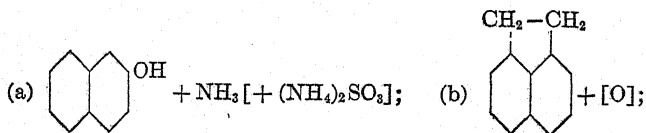
4. Predict the products obtained from the monosulfonation of the following:



5. Outline reactions starting with naphthalene for the preparation of the following compounds: 2-naphthoic acid,  $\beta$ -bromonaphthalene,  $\alpha$ -naphthoquinone, naphthionic acid.

6. Compare the reactions with halogens, reducing agents, and oxidizing agents of benzene, naphthalene and anthracene, and account for the differences noted. Include specific facts.

7. Write equations for the following reactions:



8. Outline the steps in preparing anthraquinone starting with naphthalene and benzene. How would you synthesize 2-bromoanthraquinone starting with the same materials?

9. Outline the steps in the synthesis from coal tar of the following: diphenic acid,  $\beta$ -anthraquinone sulfonic acid, 1-methylanthraquinone,  $\beta$ -naphthylamine, 2-naphthol-6-sulfonic acid, 1-aminonaphthalene-6-sulfonic acid, 2-amino-6-sulfonic acid.

## CHAPTER XXVI

### ALICYCLIC COMPOUNDS

Having considered some typical representatives of aromatic hydrocarbons and their derivatives, we shall devote a chapter to a consideration of saturated and unsaturated alicyclic compounds. These substances are of interest because of certain peculiarities connected with the smaller rings, because of a type of stereochemical isomerism which occurs in ring compounds, and finally because of the large number of natural products which contain alicyclic rings. A few of the more interesting of these natural products, which include one vitamin and the sex hormones, will be considered in the next chapter.

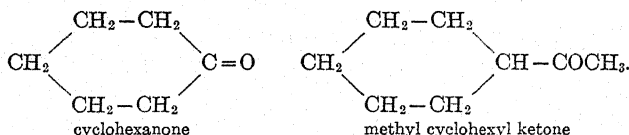
**The Cycloparaffins and Their Derivatives.** The simplest representatives of the alicyclic compounds are the cycloparaffins which have already been mentioned in connection with petroleum (p. 41). These substances are isomeric with the ethylenic hydrocarbons and have the general formula  $C_nH_{2n}$ . Two hydrogen atoms are missing as compared with the corresponding paraffin hydrocarbon,  $C_nH_{2n+2}$ ; these may be considered as having been removed in the formation of the ring. The table which follows gives the names and physical properties of some of the simpler cycloparaffins.

PHYSICAL PROPERTIES OF SOME SIMPLE CYCLOPARAFFINS

NAME	FORMULA	FREEZ- ING POINT	BOIL- ING POINT
Cyclopropane	$(CH_2)_3$	-126.6°	-34°
Cyclobutane	$(CH_2)_4$	-80°	-15°
Cyclopentane	$(CH_2)_5$	below -80°	49°
Cyclohexane	$(CH_2)_6$	6.5°	81°
Cycloheptane	$(CH_2)_7$	-12°	119°

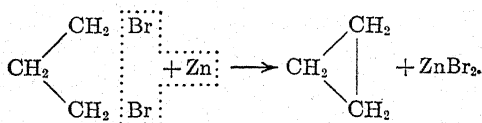
**General Characteristics of Alicyclic Compounds.** With the exception of cyclopropane (the first member of the series), the characteristic reactions of the alicyclic compounds are very close

to those of the aliphatic; to a large extent we can transfer our knowledge gained in the one field to the other. We shall consider some peculiarities of cyclopropane compounds shortly, but shall first turn to the more general behavior of the other cycloparaffins and their derivatives. Just as we have alcohols, ketones, etc., which are derived from the paraffin hydrocarbons, so we have similar groups of alicyclic compounds. In general, the characteristics of the functional groups are unchanged by being attached to alicyclic groups. With such compounds as the ketones the functional group may be a part of the ring or may be attached to an alicyclic residue. Thus, for example, we may have a cyclic ketone (*e.g.*, cyclohexanone) or a compound in which the ketone group is attached to a ring (*e.g.*, methyl cyclohexyl ketone):

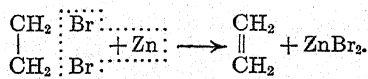


It is evident that such groups as the aldehyde group and carboxyl group in which the terminal carbon atom of a chain is always involved can not be incorporated directly in a ring.

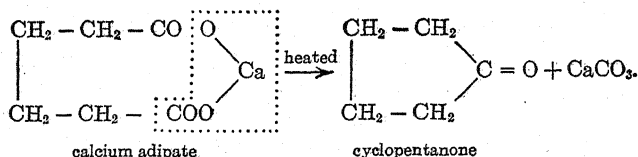
**Methods of Closing an Alicyclic Ring.** Cyclic paraffins which contain not more than six carbon atoms in the ring can be prepared by the action of metals on dihalides of the general formula  $(\text{CH}_2)_n\text{X}_2$ . This is illustrated by the formation of cyclopropane from trimethylene bromide:



The analogy between this reaction and the formation of an ethylenic compound from a dihalide having halogen on *adjacent* carbon atoms is evident:

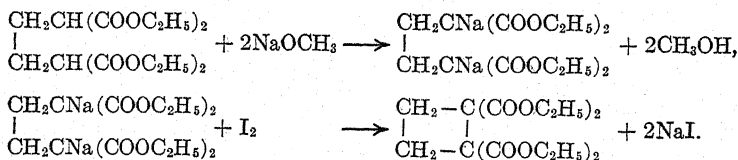


The cyclic ketones containing *five* and *six* atoms in the ring are readily prepared by heating the calcium salts of the corresponding dibasic acids. This is illustrated by the formation of **cyclopentanone** from adipic acid (p. 196):



The preparation of ketones with large rings is difficult, and until recently it was believed that the usual methods could not yield compounds with more than eight atoms in the ring. This we now know to be erroneous, as cyclic ketones containing as many as thirty-four atoms in the ring have been prepared by heating the thorium salts of dibasic acids and also by an internal condensation of dinitriles.

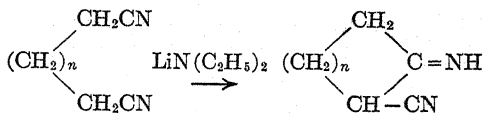
A third method of preparing the alicyclic compounds is to make use of a reaction which was discussed in connection with malonic ester. It will be recalled that by the interaction of iodine and the sodium derivative of malonic ester two malonic ester residues may be united (p. 241). If now the two malonic ester residues are a part of the same carbon chain, the result of the application of such a method will be the formation of an alicyclic ring. The following example will serve to illustrate this method:



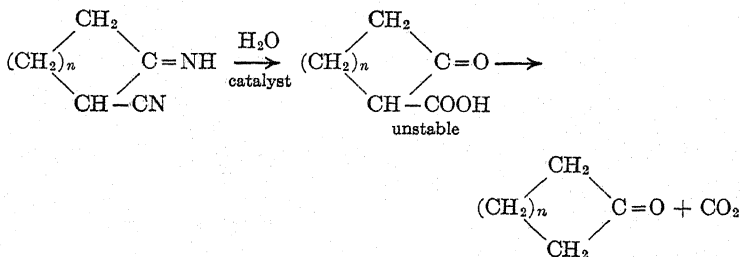
In the above equations, the formulas of the disodium derivative have been written with the sodium atoms attached to carbon atoms merely for convenience of representation; the sodium is probably attached to an oxygen atom (see p. 239).

The internal condensation of dinitriles in the presence of such strong basic catalysts as the metallic derivatives of substituted ammonias has recently proved to be a valuable method of prepar-

ing cyclic ketones with large rings. The reaction may be represented by the following general equation:

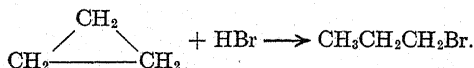


The resulting compound on hydrolysis yields a  $\beta$ -ketonic acid which, like acetoacetic acid, easily loses carbon dioxide, giving the cyclic ketone:



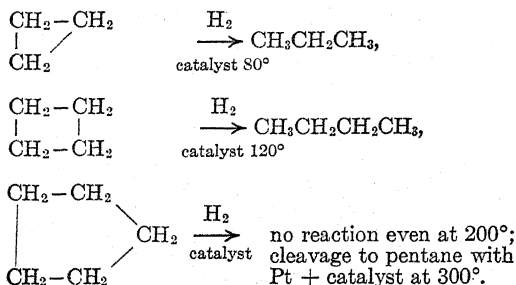
In order to prevent the interaction of *two* molecules with each other and to favor *internal* reactions between the two nitrile groups of one molecule, the concentration of the dinitrile is kept very low (*i.e.*, the reaction mixture is kept very dilute). Under these conditions very good yields of the cyclic compounds may be obtained.

**Opening the Ring in Alicyclic Compounds.** With alicyclic compounds there is always the possibility of a reaction in which some reagent combines with the molecule by opening the ring. For example, cyclopropane reacts thus with hydrobromic acid:



The individual compounds differ enormously in the rate at which such reactions proceed and the conditions which are necessary in order to bring them about. Many cyclopropane compounds are extremely reactive and the ring opens easily. Other cyclic compounds with larger rings rarely enter into such reactions.

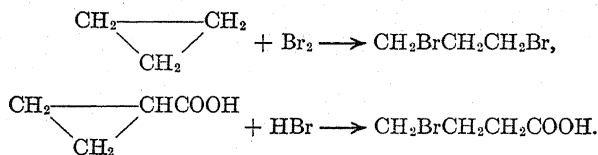
For example, cyclopropane is hydrogenated to propane by hydrogen and a catalyst at 80°, while cyclobutane with the same catalyst requires a temperature of 120°. *Larger rings in alicyclic hydrocarbons are not opened by hydrogenation under usual conditions (below 200°):*



The amount of heat evolved in these and similar hydrogenation processes may be calculated from the heats of combustion of the cycloparaffins and the corresponding open-chain compounds. It may be calculated that about 25–30 kg. cal. are liberated in opening a cyclopropane or cyclobutane ring by hydrogenation. About the same amount of heat is usually developed in adding two hydrogen atoms to an ethylenic linkage. From the standpoint of the energy relations, there is no very great difference between a double linkage or a three or a four carbon ring. On the other hand, it can be calculated that if the hydrogenation of cyclopentane, cyclohexane, or cycloheptane could be accomplished, only about 14 kg. cal. of heat would be evolved. This same small amount would also be liberated if it were possible to break a carbon chain by hydrogenation (e.g.,  $\text{CH}_3\text{CH}_3 + \text{H}_2 \longrightarrow 2\text{CH}_4$ ). This indicates that in rings containing five or more carbon atoms the valence forces are essentially those in an open chain compound. The results of a study of the energy relations, like the experimental facts concerning the ease of catalytic hydrogenation, place cyclobutane and cyclopropane (and their derivatives) in a class apart from the other alicyclic compounds.

**Cyclopropane (Trimethylene).** Cyclopropane is made from trimethylene bromide and sodium or zinc. It has excellent anesthetic properties, but its high cost of production prevents its wider use in surgery.

In cyclopropane itself and many of its derivatives, the ring is opened even when the compounds are treated with such reagents as bromine and hydrobromic acid at room temperature:



Such cleavages of alicyclic rings also occur with cyclobutane and its derivatives, but not with the larger rings unless groups are present which cause the cleavage of even open-chain compounds.

**Baeyer's Strain Theory.** Somewhat more than a generation ago, chemists were much impressed by the number of derivatives of cyclopentane and cyclohexane which were found in nature and which were readily prepared in the laboratory. They were

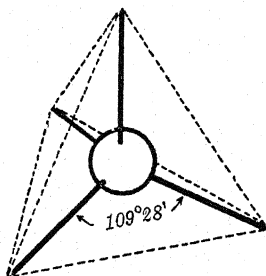


Fig. 29. Diagram showing normal valence angles of a carbon atom.

familiar not only with the fact that the preparation of cyclic ketones is particularly successful in the case of cyclopentanone and cyclohexanone, but also with the ease with which heterocyclic compounds containing five- and six-membered rings were formed. We have encountered a number of such instances in previous chapters; for example, only gamma and delta hydroxy acids readily form lactones (p. 213); in the case of the dibasic acids, only cyclic anhydrides with five- or six-membered rings can be formed directly (p. 203). Even if three- or four-membered rings are formed they are usually readily opened by some reagents.

As an explanation of all these facts, Baeyer<sup>1</sup> in 1885 suggested his strain theory. He started with the regular tetrahedral carbon atom which had already provided an adequate explanation of stereoisomerism. In this atom the four valence forces are directed from the center to the corners of a regular tetrahedron, and therefore form an angle of  $109^{\circ} 28'$  with each other (Fig. 29). In the union of two atoms, Baeyer assumed that these valence forces must lie joined in a straight line between the centers of the atom. If this assumption is correct, it is easy to see that a three-membered carbon ring can only be formed by a distortion of the valence angles of the carbon atoms. This is illustrated by the diagram shown in Fig. 30. The distortion or displacement of the valence angle can be calculated

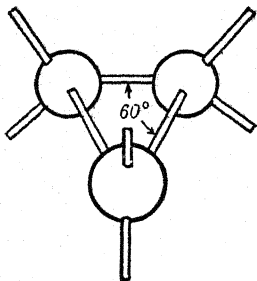


Fig. 30. Drawing of a model representing a cyclopropane ring.

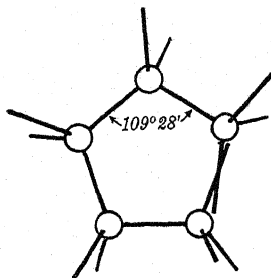


Fig. 31. Diagram showing the close approach of the terminal atoms of normal pentane when all the carbon atoms lie in a plane.

by simple geometry as  $24^{\circ} 44'$ ; in the case of the cyclobutane ring, the distortion is less ( $9^{\circ} 44'$ ) and in a cyclopentane ring, the distortion is less than a degree ( $44'$ ). The cyclopentane ring can thus be closed without appreciable distortion; this is shown in the diagram (Fig. 31) of a model of a five-membered chain *so manipulated as to bring the terminal atoms as near together as possible*. It is clear that the ends of a five-carbon chain can approach very close to each other without any distortion of the valence bonds; this, of course, is not the case with a four- or three-membered chain. Baeyer supposed that the distortion of the valence angles in the three- or four-membered rings caused a *strain* in the molecule. Because of this strain many of these

<sup>1</sup> Adolph von Baeyer (1845-1917). Professor of Chemistry at the University of Munich for more than forty years.

compounds readily combined with reagents with an opening of the ring, a condition which relieved the strain. This portion of Baeyer's theory is in accord with all the facts known today, and appears well founded, although the real physical nature of the valence strain is unknown. Baeyer also included ethylenic compounds in his theory, and accounted for their reactivity by the fact that the two valence bonds had to be distorted until they were paralleled. This large distortion ( $54^{\circ} 44'$ ) Baeyer believed was responsible for the rapidity with which ethylene and its derivatives combine with many reagents.

**Strainless Rings.** In regard to rings containing more than five atoms, Baeyer made an assumption which has proved to be erroneous. He assumed that all the atoms in any ring were in one plane. If this were true, it would be necessary to expand the valence angles in making a cyclohexane or larger ring (opposite distortion than that required for small rings). In fact, very large

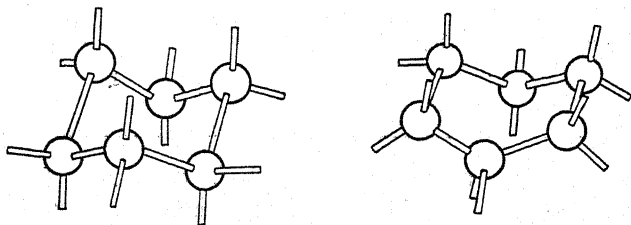


Fig. 32. Drawing of models representing two phases of a strainless cyclohexane ring. (The two phases are readily interconvertible by an oscillation of the atoms and, therefore, do not represent isomeric forms.)

rings would involve an almost unbelievable stretching. As a matter of fact, we now know that in cyclohexane and compounds containing still larger rings, the atoms do not lie in a plane. Therefore there is no strain in the cyclohexane or the larger rings.

**Cyclic Ketones with Large Rings.** The most striking work which has shown the existence of very large rings has been the preparation of a series of cyclic ketones by heating the thorium salts of dibasic acids and by condensation of dinitriles, as mentioned in an earlier paragraph. The following table lists some of the ketones thus prepared:

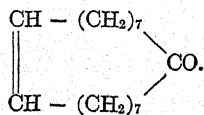
## HIGHER ALICYCLIC KETONES

NAME	FORMULA	MELTING POINT	BOILING POINT
Cyclooctanone	$  \begin{array}{c}  (\text{CH}_2)_3 \\  \diagup \quad \diagdown \\  \text{CH}_2 \quad \text{C} = \text{O} \\  \diagdown \quad \diagup \\  (\text{CH}_2)_3  \end{array}  $	—	74° (12 mm.)
Cyclononanone	$  \begin{array}{c}  \text{CH}_2 - (\text{CH}_2)_3 \\    \quad \quad \diagdown \\    \quad \quad \text{C} = \text{O} \\    \quad \quad \diagup \\  \text{CH}_2 - (\text{CH}_2)_3  \end{array}  $	—	93–95° (12 mm.)
Cyclodecanone	$  \begin{array}{c}  (\text{CH}_2)_4 \\  \diagup \quad \diagdown \\  \text{CH}_2 \quad \text{C} = \text{O} \\  \diagdown \quad \diagup \\  (\text{CH}_2)_4  \end{array}  $	—	100° (12 mm.)

The largest cyclic ketone so far synthesized contains 34 carbon atoms in a ring. In their properties these ketones show no essential differences from aliphatic compounds. From them by reduction, the corresponding secondary alcohols and finally the cyclic hydrocarbons may be prepared. In this way, for example, cyclotriacontane,  $\text{C}_{30}\text{H}_{60}$ , a solid melting at 56°, may be prepared from the corresponding cyclic ketone.

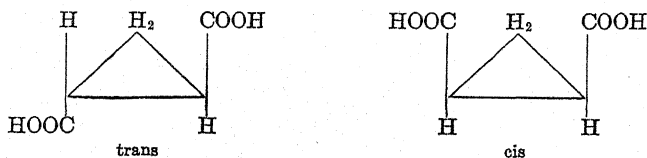
When the compounds with large rings are once formed, they are perfectly stable, and the ring can not be opened any more readily than an open chain can be cleaved.

A very interesting cyclic ketone with a 17-membered ring occurs in nature as the chief constituent of the natural, odoriferous material known as civet. This ketone is known as civetone, and has been proved to have the following formula:



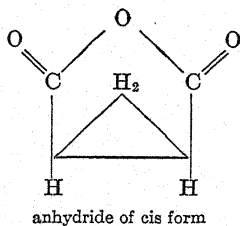
The isolation of this ketone and the proof of its structure by Ruzicka led this same investigator to attempt the preparation of cyclic ketones with large rings. The striking results of this study have just been discussed.

**Stereochemistry of Cyclic Compounds.** If a cyclic compound is asymmetrical, it can exist in two mirror images which correspond to two optical isomers, a dextro and a laevo form. Many such cyclic compounds have been resolved. If we construct a model of cyclopropane in which we substitute two hydrogens by two carboxyl groups it is easy to see that in one case we have a compound in which the two carboxyl groups lie on the same side of the ring and in the other case on opposite sides:



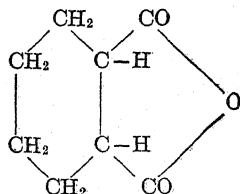
These two formulas represent two different compounds and, following the nomenclature used with geometrical isomers (p. 286), they are called *cis* and *trans* isomers. It should be noted that in the formulas printed above the carbon atoms of the ring are omitted; this is frequently done in writing the formulas of cyclic compounds.

Just as in the case of fumaric and maleic acids, one of these acids easily loses water on heating and forms an anhydride. In this case we have two rings joined together, — a carbon ring and a carbon-oxygen ring:



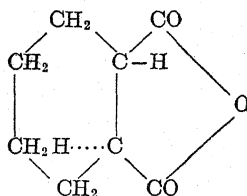
In the corresponding acid derived from cyclohexane (cyclohexane 1, 2-dicarboxylic acid), we find that again we have a *cis* and a *trans*

form, but here *both* substances lose water and form two different anhydrides, both containing two rings.



Anhydride of *cis*-cyclo-hexane dicarboxylic acid.

Both hydrogen atoms attached to the middle carbon atoms lie on the same side of the double ring system.

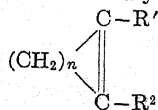


Anhydride of *trans*-cyclo-hexane dicarboxylic acid.

The two hydrogen atoms attached to the middle carbon atoms extend on different sides. One lies above, the other (shown with a dotted line) lies below a plane passing through the general direction of the exterior of the two rings.

The difference in behavior between cyclopropane and cyclohexane in this regard is due to the fact that the cyclopropane ring must by necessity have the three carbon atoms in a plane, and is rigid. In the cyclohexane ring we are dealing with a more flexible system. The carbon atoms do not lie in one plane, and therefore the two carboxyl groups may be near enough to each other in space in both the *cis* and *trans* compounds so that in either case a new ring may be formed by loss of water. This can only be made evident by a study of the models themselves, and the student who is interested is advised to construct such models. The existence of anhydrides of both *cis* and *trans* cyclohexane 1, 2-dicarboxylic acid,  $C_6H_{10}(COOH)_2$ , is conclusive evidence that the atoms of the cyclohexane ring do not lie in a plane.

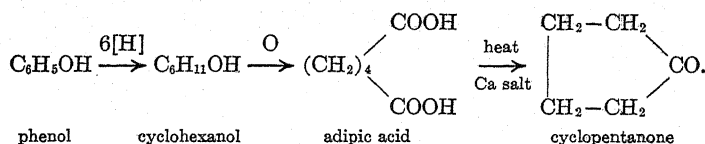
It is worthy of note that the stereochemistry of compounds of the type



is similar to that of acetylene derivatives (p. 289); only one form is possible. A construction of a model will make this evident.

**Alicyclic Compounds from Aromatic Compounds.** In recent years, the catalytic hydrogenation of aromatic compounds under pressure at elevated temperatures has made possible the industrial preparation of certain alicyclic compounds. For example, cyclohexane,  $C_6H_{12}$  (also known as hexahydrobenzene), may be thus prepared from benzene,  $C_6H_6$ , and cyclohexanol,  $C_6H_{11}OH$ , from phenol,  $C_6H_5OH$ . Such methods often provide the most convenient way of preparing alicyclic compounds, if the corresponding aromatic compound is readily available.

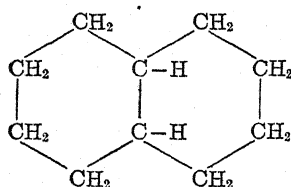
The vigorous oxidation of alicyclic alcohols, ketones, or unsaturated compounds, results in the opening of the ring. This occurs in rings of any size just as similar reactions cause the cleavage of open chains. The oxidation of cyclohexanol provides a relatively cheap method of preparing adipic acid. From this, in turn, cyclopentanone may be prepared. Thus, it is possible to synthesize even a five-membered ring compound from phenol by the following series of reactions:



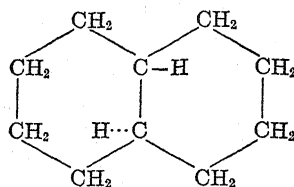
**Hydrogenated, Polycyclic, Aromatic Compounds.** Naphthalene and its derivatives may be hydrogenated by means of hydrogen gas and a suitable catalyst. The completely hydrogenated compounds contain ten more hydrogen atoms than the parent substance. They are therefore known as the **decalins** (decahydro naphthalenes). A completely hydrogenated aromatic compound is also sometimes designated as a **perhydro compound**. Thus, decalin,  $C_{10}H_{18}$ , might be called perhydronaphthalene. Completely hydrogenated phenanthrene,  $C_{14}H_{24}$ , is given the name perhydrophenanthrene. We shall see in the next chapter that this system is the skeleton of a large and varied group of natural products of great biochemical importance.

Decalin can exist in two stereochemically isomeric forms. The case is very similar to that of the anhydrides of the two cyclohexane dicarboxylic acids except that the second ring is a carbon ring and not an oxygen-containing anhydride ring. The construction of models with strainless rings will help in understanding this

type of stereoisomerism. On paper the two isomers may be represented by using the convention that the hydrogen atoms attached to the middle carbon atoms are written with a heavy line if they extend above the paper and a dotted line if below:

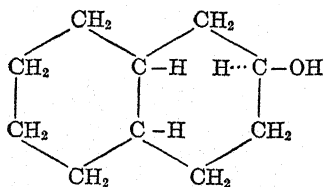


cis decalin  
(b.p. 193°)

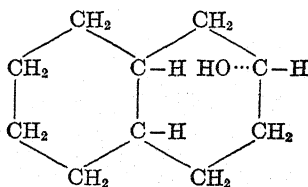


trans decalin  
(b.p. 185°)

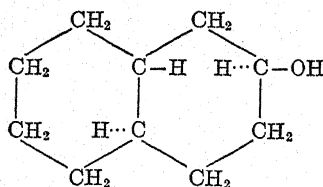
When one of the  $\text{CH}_2$  groups in decalin carries a substituent, four stereoisomers are possible. In the case of perhydro  $\beta$ -naphthol (2-decalol) all four isomers have been isolated. Using the same conventions in regard to the representation of three-dimensional formulas on paper, we may write their formulas as follows:



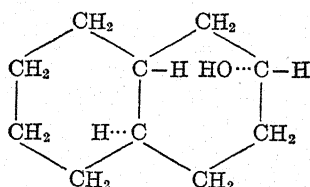
m.p. 105°



m.p. 17°



m.p. 75°



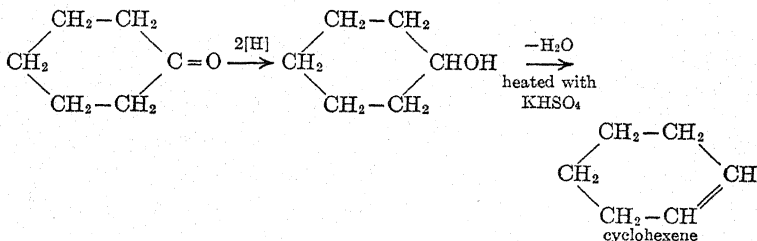
m.p. 53°

The first pair of isomers may be considered as derived from cis decalin; the other pair from trans decalin. This type of isomerism is very common among complex alicyclic compounds.

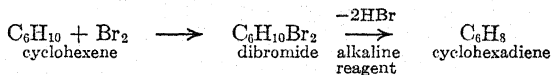
If the molecule of such a cyclic stereoisomer is asymmetric (p. 223), the

compound may exist in a right- and left-handed modification and be separable into optical isomers. When such substances occur in nature, usually only one of the two enantiomorphs (optical isomers) is found, the substance being optically active. When the substance is prepared in the laboratory from inactive material, the racemic mixture, of course, results.

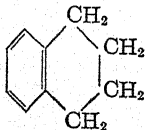
**Unsaturated, Alicyclic Compounds.** The method of preparation of unsaturated alicyclic compounds follows the general methods considered in the case of open-chain compounds. For example, we may prepare a six-membered ring containing one double bond by the following series of reactions. The resulting compound is called cyclohexene, the nomenclature following that of the open-chain compounds, except that the prefix "cyclo" is added in all cases:



Cyclohexene may be transformed into cyclohexadiene (p. 329) by the following reactions:



The hydrogenation of benzene can not be controlled so that such intermediate products as cyclohexadiene or cyclohexene may be isolated. The reason for this lies in the low affinity of benzene for one mole of hydrogen (p. 330). Corresponding to the greater affinity of naphthalene towards various reagents and to its less pronounced aromatic nature, we saw (p. 451) that naphthalene can be reduced by sodium amalgam so that only two hydrogen atoms are added. Similarly, by catalytic reduction a series of partially hydrogenated naphthalenes can be obtained. The tetrahydro compound which contains one saturated alicyclic and one aromatic ring is known as tetralin.



Both tetralin and the mixture of the two decalins are high boiling liquids. Since they can be prepared cheaply from naphthalene by catalytic hydrogenation they are used often, both in the laboratory and in industry.

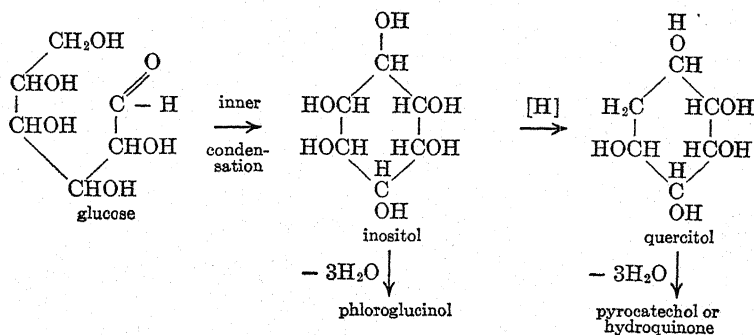
**Dehydrogenation of Alicyclic Compounds.** Unsaturated, alicyclic compounds which differ from the corresponding aromatic compounds by only two hydrogen atoms, easily lose these atoms in the presence of such catalysts as palladium, platinum, or nickel, and yield the aromatic hydrocarbon (*e.g.*, cyclohexadiene  $\rightarrow$  benzene, p. 330). Saturated, alicyclic compounds and those containing only one double bond per ring are transformed with more difficulty to the corresponding aromatic hydrocarbon. Since such transformations are often of great assistance in elucidating the structure of alicyclic compounds found in nature, they have been extensively used. It has been found that selenium is in many cases the best reagent. High temperatures are employed and the hydrogen is evolved as hydrogen selenide ( $\text{H}_2\text{Se}$ , corresponding to  $\text{H}_2\text{S}$ ). Sulfur may also be employed. Migration of alkyl groups or even the opening and closing of rings, however, sometimes occurs. In spite of these abnormalities the reaction has been of great value in studying some of the substances to be considered in the next chapter.

**Opening of Alicyclic Rings.** Aside from cyclopropane and a few cyclobutane derivatives, the alicyclic ring is not readily opened by reagents. In fact, the problem is exactly analogous to cleaving a saturated hydrocarbon chain and no practical methods for doing this are known. The determination of the structure of a fully saturated alicyclic compound, like the determination of the structure of a paraffin hydrocarbon is obviously a matter of great difficulty. Dehydrogenation to an aromatic compound is about the only possibility. If one or more double bonds, hydroxyl or ketone groups are present, however, the ring may be opened by oxidation. For example, cyclohexene on oxidation yields  $(\text{CH}_2)_4(\text{COOH})_2$ , adipic acid; cyclohexanol, the secondary alcohol, and cyclohexanone behave in the same manner (p. 481). Cyclopentanone under similar conditions yields glutaric acid. If in this way the substance can be transformed into compounds of known structure, valuable evidence as to the original structure is obtained. In the case of a complex substance containing several rings the dibasic acid formed may be unknown but the

carboxyl groups give a point of attack for coming down the series (p. 437) and the degradation may be continued.

**Alicyclic Polyhydroxy Compounds.** A group of interesting and important polyhydroxy alicyclic compounds are found in plants and animals. The two most important of these are **quercitol** or **quercite**,  $C_6H_7(OH)_5$  (pentahydroxycyclohexane), and **inositol** or **inosite**,  $C_6H_6(OH)_6$  (hexahydroxycyclohexane). The latter occurs in an inactive (internally compensated) form, as well as a dextro and a laevo form. Monomethyl ethers of inosite also occur in certain plants, but the most important derivative is the hexaphosphoric ester,  $C_6H_6(OPO_3H_2)_6$ , known as **inosite-phosphoric acid**. It occurs very widely distributed in plant cells and in relatively large amounts in steep water of corn. It is usually isolated as the acid calcium-magnesium salt which is known as **phytin**. The phosphoric acid residues are easily removed by hydrolysis with acid or by the action of a specific enzyme. Inositol seems to occupy an intermediate position in nature between the sugars and the aromatic compounds.

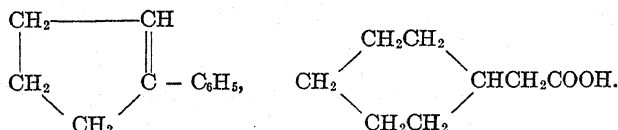
It has been suggested that inositol is formed in nature by a cyclic condensation of glucose somewhat analogous to the aldol condensation. One might imagine that by reduction of inositol, quercitol would result. It is also conceivable that these two alicyclic polyhydroxy compounds are the precursors of the aromatic polyhydroxy compounds which are found in nature (p. 393). A hypothetical mode of formation of cyclic polyhydroxy compounds in nature may be represented as follows:



## QUESTIONS AND PROBLEMS

1. Write structural formulas for: cyclopentene, cyclononane, cycloheptanone, 1, 1-dimethyl-cyclopropane, ethyl cyclopentyl ketone, 1, 3-cyclohexadiene, 1, 4-cyclohexadiene, tetrahydronaphthalene, decalin.

2. Outline the steps in the synthesis from phenol or benzene of: cyclohexene, cyclopentanol,



3. If 2-methylnaphthalene is hydrogenated to the perhydro compound, how many stereoisomers would you expect to obtain? How could these compounds be converted back to methylnaphthalene? How many stereoisomeric perhydrophenanthrenes are theoretically possible?

4. Outline the steps in two different methods of preparing cyclooctane from trimethylene glycol.

5. Isophthalic acid (benzene-1, 3-dicarboxylic acid) does not form a cyclic anhydride. The hexahydro compound formed from it by catalytic hydrogenation, on the other hand, forms a cyclic anhydride when treated with dehydrating agents. Explain.

6. Write equations illustrating two methods of closing a three-membered carbon ring, and two methods of opening such a ring.

7. Predict what reactions (if any) would occur when the following compounds are treated with concentrated hydrobromic acid: cyclopropane, cycloheptanol, cyclooctene, cyclodecane.

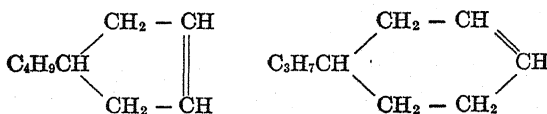
8. What is meant by the term "strainless ring"? What conclusions may be drawn from the fact that large ring compounds can not be opened except by drastic treatment? How can one account for the fact that compounds with large rings are difficult to prepare by methods which give good results in forming five- and six-membered rings?

9. The anhydride of trans hexahydrophthalic acid on heating readily passes over into the anhydride of the cis form. The isomeric decalols are not changed by heating to even higher temperatures and for longer periods of time. What mechanism of the conversion of the stereoisomeric anhydride might account for the ease of its isomerization as compared with such substances as the decalols?

10. Cyclohexanone readily forms an oxime which when treated with concentrated sulfuric acid or phosphorus pentachloride and then alkali yields  $\epsilon$ -aminocaproic acid,  $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ . Indicate the transformations involved during these reactions. What rearrangement is involved?

11. A compound is known to be represented by either one of the two fol-

lowing formulas; by what reactions would you be able to establish which formula is correct?



By what steps could you prepare the cyclopentene compound, starting with malonic ester?

12. A mixture of the four 2-decalols was oxidized with chromic acid to give the corresponding ketones. How many isomeric products would you expect?

## CHAPTER XXVII

### NATURAL PRODUCTS CONTAINING ALICYCLIC RINGS: TERPENES, STEROLS, SEX HORMONES

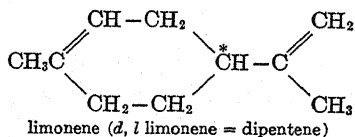
A great variety of substances which possess alicyclic rings are found in nature. The simplest of these contain a six-membered ring and occur principally in plants. Others contain partially hydrogenated naphthalene rings, and several different classes of important compounds contain a reduced phenanthrene nucleus. A very brief summary of some of the more interesting representatives will be given in the following pages.

#### CYCLIC TERPENES

An interesting group of unsaturated alicyclic compounds with the formula  $C_{10}H_{16}$  are found widely distributed in certain plants. They are known as the **cyclic terpenes**. They occur in essential oils, particularly those obtained from citrus fruits. They also occur in oil of turpentine and similar materials made from coniferous trees. Certain cyclic alcohols and ketones closely related to the cyclic terpenes are also found in the plant world. Since a number of these compounds are of considerable practical importance and have been the subject of a great deal of investigation, they will be briefly considered in the following pages.

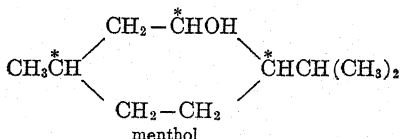
**Limonene.** Limonene,  $C_{10}H_{16}$ , occurs in two optically active forms, a dextro compound which is present in many essential oils from citrus fruits, and a laevo limonene which can be obtained from the leaves of certain pines. The racemic compound, known as **dipentene**, can be prepared in the laboratory either by a complete synthesis or by a transformation of certain other terpenes. Dipentene is also formed along with other products by heating isoprene at  $300^{\circ}$ ; in this reaction two isoprene molecules combine with each other. These compounds are liquids (b.p.  $177^{\circ}$ ). As the following formula shows, they are derivatives of cyclohexene; one methyl group and an unsaturated side chain containing three carbon atoms are attached to the opposite extremities of the ring. The asymmetric carbon atom is denoted by a star.

As would be expected, the two double bonds react with a variety of reagents.



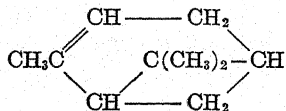
The nature of the carbon skeleton in limonene was first established by converting it into the aromatic hydrocarbon known as *para cymene* (p. 339). This was done by bromination and subsequent elimination of hydrobromic acid. The structure of cymene was readily established by the methods employed in aromatic chemistry. Subsequently, dipentene itself was synthesized from a cyclohexanone derivative of known structure.

**Menthone and Menthol.** Two oxygen-containing substances closely related to limonene occur in certain essential oils. One of these is a saturated alcohol, **menthol**,  $\text{C}_{10}\text{H}_{20}\text{O}$ , which is the chief constituent of peppermint oil. Associated with it is the corresponding ketone, **menthone**,  $\text{C}_{10}\text{H}_{18}\text{O}$ . Menthol is a solid melting at  $43.5^\circ$ , while menthone is a liquid boiling at  $207^\circ$ . Both of these substances have a strong peppermint odor and are laevo-rotatory. The asymmetrical carbon atoms in the menthol molecule are indicated by stars below. It will be noted that menthol is an hydroxyl derivative of the completely hydrogenated limonene molecule. The characteristic reactions of the hydroxyl group and the ketonic group are shown by menthol and menthone respectively.



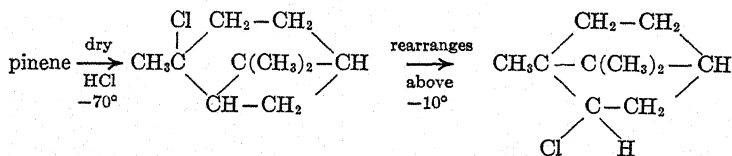
**Pinene.** Pinene,  $\text{C}_{10}\text{H}_{16}$ , is the principal constituent of turpentine oil. It occurs in two forms, the dextro in American turpentine and the laevo in European turpentine. Turpentine is manufactured from the sap of coniferous trees by a distillation process. It is widely used as a solvent in the paint industry.

The structure of pinene is as follows:



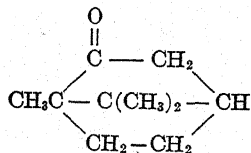
It will be noticed that this compound contains two rings and is thus known as a **dicyclic compound**. One of the rings is a cyclobutane ring, the other a cyclohexene ring. Pinene is a colorless oil boiling at  $156^{\circ}$ . It combines with one molecule of hydrochloric acid, yielding a crystalline solid known as **pinene hydrochloride**,  $C_{10}H_{17}Cl$ . The nomenclature of this compound is unfortunate, as the compound is not a hydrochloride in the sense in which this term is used to describe the salts of bases; it is really a chloro derivative of a saturated dicyclic compound. During the addition of hydrogen chloride a rearrangement of the cyclobutane ring to a cyclopentane ring occurs. This rearrangement was for a long time the cause of a great deal of confusion in regard to the structure of pinene and its derivatives. Pinene hydrochloride has a camphor-like odor and is known as **artificial camphor**. It is not to be confused, however, with true synthetic camphor.

At  $-70^{\circ}$  pinene combines with dry hydrogen chloride without rearrangement. The halogen acid adds to the double linkage according to Markownikoff's rule. The tertiary halide thus formed rearranges at  $-10^{\circ}$  or higher temperatures; in this process the bridge ring enlarges:



The final product "pinene hydrochloride" is properly called **bornyl chloride** (see below).

**Camphor.** Camphor,  $C_{10}H_{16}O$ , is a ketonic derivative of a saturated dicyclic hydrocarbon. The structural formula is:

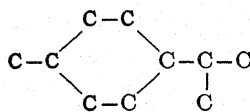


It will be noted that this formula is similar to that of pinene, but that the enclosed ring is five-membered, and not four-membered. Camphor (often called Japan camphor) is obtained by the steam distillation of the wood, twigs, and leaves of the camphor tree (*laurus camphora*). It is produced almost entirely in the Orient. The form which occurs in the camphor tree is dextro-rotatory,

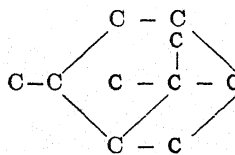
and it is obtained as colorless crystals with a very characteristic odor (m.p.  $175^{\circ}$ , b.p.  $204^{\circ}$ ). It has been used in medicine in small amounts for a great many years, and is now used in very large quantities in the manufacture of celluloid (p. 319). It may be prepared by a series of chemical transformations from pinene; the material thus prepared is the racemic form (*d,l*, camphor). The commercial synthesis of camphor from oil of turpentin produces a product which competes with the natural product.

The alcohol which corresponds to camphor is borneol,  $C_{10}H_{18}O$ , m.p.  $206^{\circ}$ . It is found naturally in certain trees in the Orient. It can be prepared by the reduction of camphor. The chemical preparation of camphor from pinene involves the preparation of bornyl chloride, the hydrolysis of this to the racemic borneol, and subsequent oxidation to the ketone.

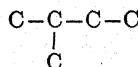
**Relation of Terpenes to Isoprene.** A very interesting relationship exists between cyclic terpenes and isoprene. This unsaturated hydrocarbon,  $CH_2 = C(CH_3)CH = CH_2$ , we have already encountered as being the fundamental building stone of the rubber molecule. If we examine the structure of the cyclic terpenes it will be seen that they all may be regarded as containing two isoprene nuclei joined together in different ways. This is illustrated in the case of the limonene and the pinene skeletons by printing the carbon atoms of one isoprene unit in heavy type. The reader can easily convince himself that a similar situation exists in regard to camphor. It will be clear that it is the occurrence of the carbon chain of isoprene which is of importance, and that different degrees of hydrogenation are obviously involved in the different terpene compounds.



carbon skeleton of  
limonene and menthol



carbon skeleton  
of pinene

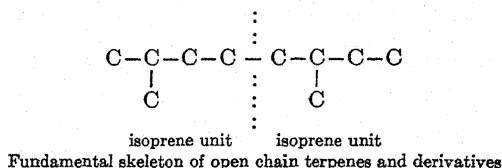


carbon skeleton  
of isoprene

**Open Chain Terpenes.** The terpenes themselves are often defined as being naturally occurring substances of the formula  $(C_5H_8)_n$ ; those with the formula  $C_{10}H_{16}$  being known as the terpenes proper, which include both open chain and alicyclic com-

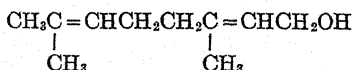
pounds. Higher terpenes are also known (p. 605), those with the molecular formula,  $C_{15}H_{24}$ ,  $(C_5H_8)_3$ , being called *sesqui-terpenes*. In Chap. XXXII we shall find the isoprene unit involved in another group of very important natural substances of which the orange pigments, carotene and xanthophyll, are representatives. The persistence of this isoprene unit is of the greatest interest; it shows there exists in nature a definite pattern which reveals itself in a great variety of plant products.

More than a dozen compounds have been isolated from essential oils which contain an open-chain carbon skeleton composed of two isoprene units and joined as shown below:



The more important of these are not terpenes themselves but oxygen-containing compounds (*i.e.*, alcohols or aldehydes). A few may be mentioned as illustration for the entire group.

**Geraniol and nerol**,  $C_{10}H_{17}OH$ , are two geometrical isomers of the following structure:



They are sweet smelling liquids with a high boiling point. Geraniol occurs in geranium oil, certain rose-oils, and citronellas. It is often associated with **citronellol**,  $C_{10}H_{19}OH$ . The latter compound differs from geraniol in that the double bond nearer to the alcohol group is hydrogenated.

**Citral** is the aldehyde which corresponds to geraniol (sometimes called geranial). It occurs in the essential oils obtained from citrus fruits, lemon grass, and eucalyptus and has a fragrant, citrus odor.

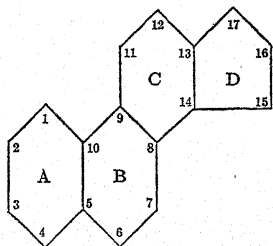
#### STEROLS AND BILE ACIDS

The sterols are a group of complex alicyclic alcohols. They are colorless, crystalline solids, soluble in organic solvents, and usually found in the unsaponifiable portion of fats (p. 183). The commonest example is **cholesterol**, which occurs widely distributed in animals, particularly in relatively large quantities in the spinal cord

and in human gall stones. The sterols which occur in plants are known as the **phytosterols**; there are a great many of these known. Esters of the sterols, as well as the free sterols, occur in plants and animals. **Lanolin**, or wool fat, is a very complicated mixture of sterols and sterol esters.

**Cholesterol.** Cholesterol is a colorless, crystalline solid which melts at  $148^{\circ}$ – $151^{\circ}$ . Like all the sterols, it is difficult to purify if it is contaminated with similar substances. The molecular formula of cholesterol is  $C_{27}H_{46}O$ . The oxygen atom is present in a secondary hydroxyl group, and there is one double bond in the molecule. The saturated parent hydrocarbon which may be obtained from it is **cholestane**,  $C_{27}H_{48}$ . As shown by its empirical formula, this hydrocarbon contains four alicyclic rings. The corresponding paraffin would be  $C_{27}H_{56}$ ; therefore, there is a deficiency of 8H or  $4H_2$ , indicating four alicyclic rings.

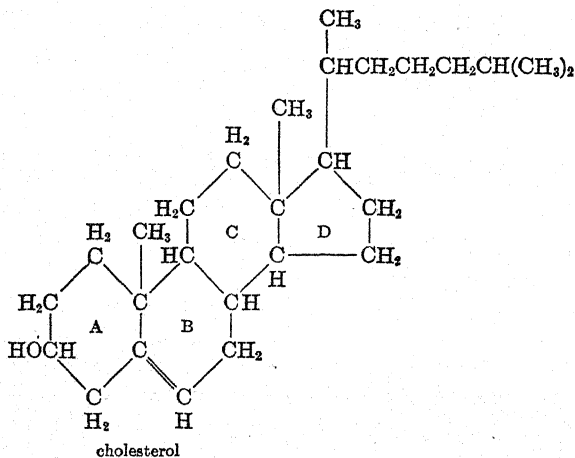
It has taken many years of patient labor by many chemists to determine the size and relative positions of the four alicyclic rings in cholesterol and the other sterols. Only within the last few years has the goal been reached, namely, the establishment of a satisfactory structural formula. It is interesting that one of the important lines of evidence was furnished by an X-ray study of the crystals of certain sterols and sterol derivatives in 1932. The dimensions of the molecule thus revealed were inconsistent with an arrangement of rings which had been favored until then. They corresponded closely, however, with those of a molecule which contained a hydrogenated phenanthrene ring to which an additional alicyclic ring had been fused. In the next few years it was clearly established that all the sterols (and as we shall see many other classes of interesting compounds as well) contain the following carbon skeleton:



This arrangement of carbon atoms corresponds to that of a hydrocarbon in which a phenanthrene nucleus (rings A, B, C) and a

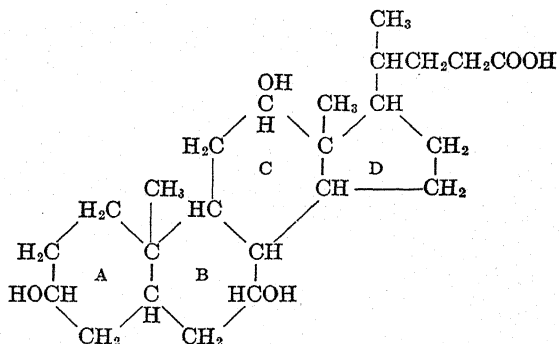
cyclopentane (ring D) have been fused together. Such a hydrocarbon, if the first three rings are aromatic and ring D a cyclopentene ring ( $\text{CH}_2$  at 15, 16, 17, double bond at 13, 14) is known as **cyclopentenophenanthrene**. Since in the sterols all the rings are alicyclic, they may be regarded as derivatives of the completely saturated compound, **perhydrocyclopentanophenanthrene**. This parent hydrocarbon can also be considered as consisting of a perhydrophenanthrene ring and a cyclopentane ring fused together, an alternative name is therefore **cyclopentanoperhydrophenanthrene**.

**Constitution of Cholesterol.** The structural formula of cholesterol is:



It will be noted that this formula contains the fused, hydrogenated phenanthrene-cyclopentane skeleton with methyl groups substituted at positions 10 and 13, a branched aliphatic chain at 17, an hydroxyl group at 3 and a double bond between atoms 5 and 6 in ring B. Almost all the sterols so far investigated differ from cholesterol only in regard to (1) the degree and position of the unsaturation (some are saturated); (2) the nature of the side chain on position 17; and (3) their stereochemical configuration. In regard to the latter point, an inspection of the formula will show that the same type of isomerism discussed in the case of the four isomeric decalols (p. 482) can occur in the case of the sterols. Indeed, because of the number of rings, the possibilities are still greater. This fact, alone, makes an elucidation of the structure of these compounds a matter of great difficulty.

**The Bile Acids.** From the bile of various species of animals, a number of hydroxy acids have been isolated. They usually occur coupled to the amino acids, glycine,  $\text{NH}_2\text{CH}_2\text{COOH}$ , or **taurine**,  $\text{NH}_2(\text{CH}_2)_2\text{SO}_3\text{H}$ , through an amide linkage; thus,  $\text{RCONHCH}_2\text{CH}_2\text{SO}_3\text{H}$ . The amide linkage is easily hydrolyzed and the unconjugated bile acids are obtained. Thus, **glycocholic acid** gives glycine (p. 576) and the bile acid, **cholic acid**. The latter,  $\text{C}_{24}\text{H}_{40}\text{O}_5$  or  $\text{C}_{23}\text{H}_{36}(\text{OH})_3\text{COOH}$ , occurs in large quantities in the bile of man and a number of animals and is the commonest representative of this class. The structural formula for cholic acid is:



Like the sterols, cholic acid and all the other bile acids contain the cyclopentanoperhydrophenanthrene skeleton. Furthermore, like the sterols, there are methyl groups in positions 10 and 13, a branched side chain in position 17 (which in this case carries a carboxyl group) and position 3 carries an hydroxyl group. Unlike cholesterol, there is no unsaturation and there are two additional hydroxyl groups in positions 7 and 12, respectively.

**Relation of Bile Acids to Sterols.** The simplest bile acid is, perhaps, **lithocholic acid** which occurs in the human bile and that of the ox in very small quantities. It contains only one hydroxyl group (in position 3). The rings are all saturated. Concerning the structural skeleton, it differs from cholesterol only in that the final isopropyl of the long side chain of the sterol is missing and the terminal group is a carboxyl group. Stereochemically, as we shall see, it differs from cholesterol in two respects: first the configuration of the OH group (position 3) and, secondly, the configuration of the union of rings A and B.

On heating the bile acids in a vacuum they lose water, forming

unsaturated acids. Thus, in the case of lithocholic acid, a double bond is introduced by this method in ring A. In the case of cholic acid, three double bonds are formed, one in each of the rings A, B, and C. All these unsaturated acids are readily hydrogenated in the usual manner and yield the same acid with four completely saturated alicyclic rings,  $C_{23}H_{39}COOH$ , **cholanolic acid**. This same acid can also be prepared by the oxidation with chromic acid of a hydrocarbon, **coprostane**,  $C_{27}H_{48}$ , which, in turn, is prepared by reduction of a certain sterol known as **coprosterol**,  $C_{27}H_{48}O$ , found in feces. In this oxidation, the terminal isopropyl group is removed (as acetone) and a  $CH_2$  group is converted to  $COOH$ . This transformation is of the greatest importance *since it relates the sterols and the bile acids*.

The hydrocarbon which is most easily obtained by reduction of cholesterol itself is known as **cholestane**; it is isomeric with coprostane. (In the reduction, the double linkage is hydrogenated first and then the secondary alcohol group replaced by hydrogen.) Cholestane on oxidation yields an acid isomeric with cholanolic acid called **allocholanolic acid**. The isomerism of coprostane and cholestane and of cholanolic and allocholanolic acid is fundamentally the same as the isomerism of *cis* and *trans* decalin (p. 482). The difference in the case at hand is due to the difference in the relative position of the hydrogen atom and the methyl group at positions 5 and 10 (*i.e.*, the positions connecting rings A and B). In almost all the sterols (except coprosterol) which have a hydrogen atom at position 5, this hydrogen atom and the methyl group at 10 are on opposite sides while in coprosterol and the majority of the bile acids they are on the same side of the fused rings A and B. The isomerism is thus exactly analogous to that of the two decalins, except that one  $CH_3$  group takes the place of one of the hydrogen atoms attached to the two central carbon atoms.

**Determination of the Structure of the Sterols and Bile Acids.** Now that the fundamental skeleton of cholesterol and the common bile acids has been unequivocally established, it is only necessary to relate any newly discovered sterol or similar compound to those substances whose structure is known. The number of possible stereoisomers is very great, as a consideration of the isomerism of decalol (p. 482) and an inspection of the formula of cholesterol will make evident. By suitable transformations, it has been possible to assign stereochemical configurations to the hydroxyl groups in the sterols and to determine the relative positions of the atoms and groups at the points of fusion of the rings. All the naturally occurring sterols and bile acids are optically

active but in no case has an enantiomorphic pair of isomers been found or as yet prepared.

Of the methods employed in elucidating the nature of the side chain, the size of the rings, and the positions of the substituents in the sterols and bile acids, one or two may be mentioned. The degradation of the side chain of the bile acids by the oxidation of tertiary carbinols formed by the action of the Grignard reagent on the esters (p. 437) proved of great value. Not only was the constitution of the side chain thus established by stepwise degradation but finally ring D itself was reached and opened by oxidation without disturbing the rest of the molecule. No single set of simple transformations can be given within the limits of this book, which, taken by themselves, prove the skeleton structure of the sterols and bile acids. One or two transformations may be mentioned, however, which, when taken with a mass of other evidence, indicate the nature of the fundamental arrangement of the carbon atoms. Selenium dehydrogenation (p. 484) of cholesterol and cholic acid gives a number of products including a hydrocarbon,  $C_{18}H_{16}$ , whose structure has been established by synthesis as a monomethylcyclopentenophenanthrene (methyl group on the five-membered ring in position corresponding to the side chain of the sterols). If this reaction were clean cut and all possibility of rearrangement or ring opening and closing were excluded, these transformations could be adduced as final evidence as to the nature of the carbon skeleton. However, dehydrogenations at high temperature have been found often to involve shifts of atoms or groups and conclusions derived solely from them are unreliable. For example, chrysene (p. 466) with four six-membered rings is also obtained by the selenium dehydrogenation of cholesterol and cholic acid, a five-membered ring D having enlarged to a six. In all these dehydrogenations the  $CH_3$  groups at the junction of the rings either split off as methane or migrates, sometimes taking part in the enlargement of ring D.

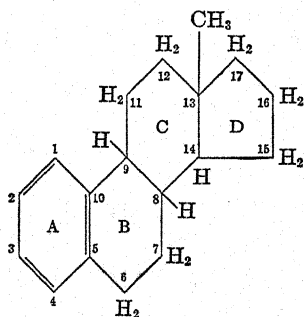
#### SEX HORMONES AND VITAMIN D

The ductless glands of the animal body secrete internally substances known as hormones. These compounds are distributed by the blood or lymph to other portions of the body whose structure or function is thereby modified. The potency of these endocrine secretions (hormones) is remarkable, a very small portion of a milligram often being effective. Different glands produce different hormones with totally different physiological action. It is not surprising that among the hormones which have been isolated we find a variety of types of compounds.

One group of substances known as the sex hormones are closely related to cholesterol and the bile acids. Structurally, they may be considered as derived from cholesterol by oxidation. Indeed, it may be that cholesterol is the actual precursor of these hormones but on this point we are still uncertain and the way the animal

body prepares these hormones is as yet unknown. The physiologist has recognized for years that the glands of the genital systems produce hormones. It is only during the last decade that by the combined labors of the physiologist, biochemist, and organic chemist the sex hormones have been isolated and their structure determined. Three different types of sex hormones originate in the gonads (testes and ovaries). They are (1) the estrogenic hormones; (2) the hormone produced by the corpus luteum which is essential for pregnancy; and (3) the male hormones that cause changes in the accessory sexual organs of the male. The production of all these hormones appears to be regulated in turn by other substances (the gonadotropic hormones produced in the anterior lobe of the pituitary). The structure of these pituitary hormones is not now known. Those of the sex hormones have been established and examples are given below.

**The Female Sex Hormones.** The hormones concerned with the estrogenic cycle and the hormone of the corpus luteum (a small yellow body in the ovary) are often designated as the **female sex hormones**. The estrogenic hormones (more than half a dozen have been isolated) may all be regarded as derived from a hydrocarbon containing one aromatic and three alicyclic rings. The structure of this hypothetical parent may be represented as follows:



For example, one of the most potent of these hormones is **estriol**, which can be isolated from the urine of pregnant women. This substance is a trihydroxy derivative of the hydrocarbon shown above, the OH groups being at positions 3, 16, and 17. In a closely related ketone, **estrone**, which occurs along with estriol, there is a ketonic oxygen attached to carbon atom 17, and an

hydroxyl at 3. (If the reader will write out such formulas, it will become evident that on dehydration estriol should readily lose water between 16 and 17, yielding the enolic form of estrone. Actually, estrone is readily formed by dehydrating estriol.) Unlike the sterol and bile acid nucleus, that of the estrogenic hormones contains one aromatic ring. The hydroxyl group in position 3 is, therefore, phenolic (weakly acidic).

In printing structural formulas for the sex hormones, sterols, and related substances, various conventions are employed to save space. Instead of showing all the carbon and hydrogen atoms (as in the formulas on pp. 494 and 498), an outline formula may be printed and, as above, the hydrogen atoms shown *except in the aromatic rings*. This convention has been long employed with the terpenes. An alternative procedure is not to print any of the hydrogen atoms but show all the double bonds including those of the aromatic rings. The possibility of confusion between this convention and the one that employs an outline ring for an aromatic compound, is evident. The reader of chemical literature must be on his guard, as three fused hexagons, for example, might signify either phenanthrene or perhydropheanthrene!

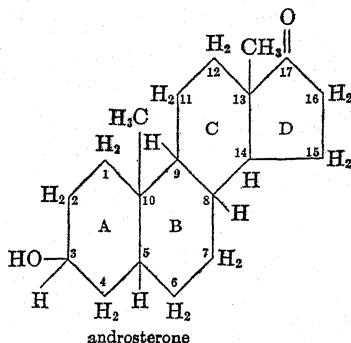
A group of hormones isolated from mare's urine has great estrogenic potency. Their structure is similar to that of estrone except that they are more highly unsaturated (double bonds in ring B). Interestingly enough, estrone has been isolated not only from urine and placenta but from a variety of vegetable sources. Certain synthetic compounds very remotely related to the hormones have been found to have estrogenic properties. Clearly, in the case of this class of hormones, many types of structure will suffice. This lack of specificity is not general among hormones or other substances with biochemical action.

On fusion with potassium hydroxide ring D in estriol is opened between the two hydroxyl groups. The resulting dibasic acid (containing now only rings A, B, C) on dehydrogenation with selenium yields dimethylphenanthrene. This same phenanthrene derivative can be obtained by the dehydrogenation with selenium of a derivative of the bile acids in which the side chain has been removed by degradation and ring D opened. These transformations not only relate the two series but yield convincing evidence of the existence of the phenanthrene skeleton.

**Progesterone**, the hormone produced by the corpus luteum, is more closely related to cholesterol than the other female hormones. In this substance ring A is still alicyclic and the methyl group at position 10 intact. A keto oxygen is at position 3 and a double bond between 4 and 5; the other rings are saturated. At position

17 there is a methyl keto group,  $\text{CH}_3\text{CO}-$ , representing a residuum of the side chain of cholesterol and the bile acids.

**Male Sex Hormones.** The most important two male hormones which can be isolated from urine and testicular extracts are **androsterone** and **testosterone**. Like progesterone, these compounds are more closely related to cholesterol than the female hormones. Androsterone contains the cholesterol structure with all four rings saturated, an hydroxyl group at 3 (secondary alcohol), and a keto oxygen at 17. In testosterone, a keto oxygen is at 3 and an hydroxyl (secondary alcohol) at 17 with a double linkage between atoms 4 and 5 in ring A. The male hormone structure seems to be much more specific than that of the estrogenic hormone.



Androsterone may be prepared from cholesterol as might be expected from the close relationship. Androsterone belongs to the same stereochemical series as the sterols in so far as the relation of the hydrogen atom and the methyl group at positions 5 and 10 is concerned, but opposite from the sterols as far as the configuration of the OH group at position 3. The normal hydrogenation product of cholesterol cannot be employed in its preparation. Instead the stereoisomer epi-dihydrocholesterol is used (epi signifies stereoisomerism due to difference in configuration at position 3). The acetate of this compound is prepared to protect the secondary alcohol group and the compound is vigorously oxidized with chromic acid. A small yield of the acetate of androsterone is thus obtained. The hormone itself is then formed by saponification. In this drastic oxidation the whole side chain is removed and replaced by a keto oxygen in position 17. There are four stereoisomeric sterols with the structure of dihydrocholesterol which differ in the configuration of the OH group at 3 and the union of rings A and B at positions 5 and 10. These isomers are exactly analogous to the four isomeric decalols (p. 482). From each of these by suitable oxidation a ketone can be obtained (in small yield) with a keto group at position 17. Of these four ketones, the one from epi-

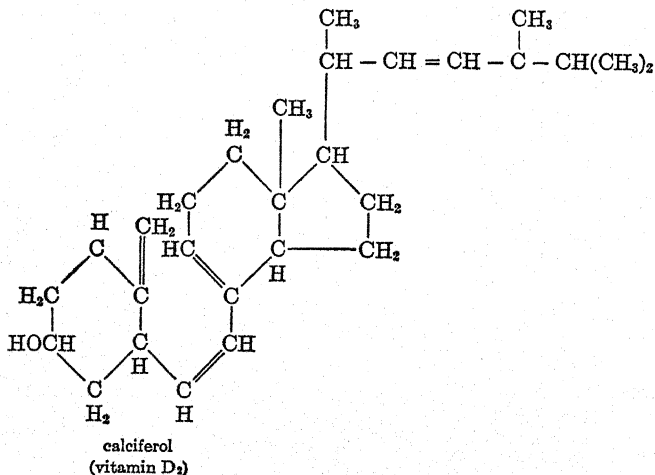
dihydrocholesterol (androsterone) is very active physiologically; the one from dihydrocholesterol is active, but only about one tenth as powerful as androsterone. The two from the sterols with the configuration at 5 and 10 characteristic of the bile acids had no physiological action even in very large doses.

**Vitamins.** Many careful experiments have shown that an animal may be fed on a diet which contains all the basal foods in a purified form, and yet the animal will fail to grow, become sick, and ultimately will die. This is true in spite of the fact that the components of the diet (purified proteins, fats, carbohydrates, mineral salts) are digested and metabolized by the animal. If now a few tenths of one per cent of certain materials are added to this diet, it becomes an entirely satisfactory ration and the animal survives. Such animal experiments form the basis of our knowledge of the accessory factors in the diet. These essentials have become known as the vitamins. By a process of repeated trial, it has been shown that there are a large number of vitamins which are necessary for a satisfactory diet; and by repeated feeding experiments, it has been possible to ascertain the concentration of these vitamins in certain foods. In several cases it has been possible to isolate them in pure chemical form and to determine their structure. When this stage of investigation has been reached, the chemistry of the vitamin (as contrasted with its biochemistry) really begins.

**Vitamin D.** This vitamin is known as the anti-rachitic vitamin. Its absence in the diet interferes with the proper formation of bone tissue and continued vitamin D-free diet thus leads to rickets.

The first clue as to the nature of vitamin D was provided by the discovery that irradiation with ultra-violet light was beneficial to rickets. It was next found that the food-stuff might be irradiated instead of the patient. As soon as this fact was established, a chemical investigation of the foods was begun to discover what particular constituent was turned into vitamin D by the action of ultra-violet light. This substance proved to be *ergosterol* which can thus be considered as a *pro-vitamin D*. This sterol on irradiation with ultra-violet light of rather long wave-length (250–300  $m\mu$ ) was transformed into a very active vitamin D. It was subsequently discovered that a still more important *pro-vitamin D* is 7-dehydrocholesterol. This substance on irradiation can be transformed into a slightly different vitamin D (vitamin  $D_3$ ).

**Vitamin D<sub>2</sub> from Ergosterol.** The conversion of ergosterol to vitamin D<sub>2</sub> proceeds in a series of steps. The first two products which are formed are biologically inactive. Further irradiation of the vitamin produces still other compounds which are inactive. The active compound which can be isolated from the irradiated ergosterol under the most favorable circumstances is known as vitamin D<sub>2</sub> or **calciferol**. It is isomeric with ergosterol but an investigation of the structure shows that ring B of the sterol system has been opened, the methyl group at position 10 being transformed into a methylene group (=CH<sub>2</sub>). Ergosterol itself differs from cholesterol slightly in regard to the side chain and is more highly unsaturated. Rings A, C, and D are saturated but there is one double bond in the side chain and two in ring B. Ergosterol also contains one more carbon atom than cholesterol due to an additional methyl group in the side chain. Apparently the unsaturation of ring B is favorable to alteration by ultra-violet light. During irradiation the ring is opened.



**Vitamin D<sub>3</sub>.** It was at first thought that the vitamin D which occurs naturally in such materials as cod-liver oil was identical with the crystalline material obtained by irradiating ergosterol. This has turned out not to be the case, however. The true vitamin in fish oils has been isolated and identified as being the same compound as can be prepared by irradiating a cholesterol transformation product called **7-dehydrocholesterol**. (Note, dehydro

indicates less hydrogen.) 7-Dehydrocholesterol is, therefore, a pro-vitamin D. 7-Dehydrocholesterol has a saturated side chain identical with that of cholesterol, saturated rings A, C, and D and, like almost all the sterols, a secondary alcohol group at position 3. There are two conjugated double bonds in 7-dehydrocholesterol just as there are in ergosterol and it is for that reason that it undergoes the same type of transformation with ultra-violet light. The vitamin D which is thus formed and which occurs in nature is called vitamin D<sub>3</sub>. If one substitutes the saturated eight-carbon side chain of cholesterol for the unsaturated nine-carbon chain of vitamin D<sub>2</sub>, the structural formula of vitamin D<sub>3</sub> results. (The name vitamin D<sub>1</sub> was given to a substance which later proved to be a mixture; only two pure vitamin Ds are known, D<sub>2</sub> and D<sub>3</sub>.)

#### OTHER COMPOUNDS OF BIOLOGICAL INTEREST CONTAINING THE CYCLOPENTENOPHENANTHRENE NUCLEUS

There are seven classes of compounds of interest to the biochemist which contain the carbon skeleton of cyclopentenophenanthrene. They are (1) the sterols, (2) the bile acids, (3) the sex hormones, (4) a group of hormones produced by the adrenal glands (known collectively as cortin), (5) the non-sugar component of certain plant glycosides which powerfully affect the animal heart (heart poisons), (6) the active principle of the venom of various species of toads (toad poisons), and (7) the non-sugar component of the saponin glycosides which occur in the digitalis family of plants. Of these classes we have considered in some detail the first three. Space permits only a word or two about the others.

**Cortin.** The crude extract obtained from the adrenal cortex which contains several hormones closely related to the sex hormones is known as cortin. In each of the hormones isolated so far, four alicyclic rings of cholesterol and the two methyl groups at positions 10 and 13 are intact. At carbon 17 a side chain of two carbon atoms is attached; this chain carries two hydroxyl groups or a ketonic and an hydroxyl group. In addition there are two other oxygen atoms in the molecule, one bound as a tertiary hydroxyl group at position 17; the other probably as a cyclic ether in a position as yet undetermined. It will be evident that these hormones are closely related to the sex hormones chemically and like

them may be formed by the organism either by oxidation of a sterol or by some mechanism in the cell which builds a sterol-like molecule with a greater degree of oxidation and fewer carbon atoms than cholesterol.

**Cardiac Aglucones.** The plant heart poisons may be illustrated by considering the glycoside digitoxin obtained by extraction of the fresh leaves of members of the digitalis family (foxglove). The crystalline glycoside, **digitoxin**,  $C_{41}H_{64}O_{13}$ , on acid hydrolysis yields three molecules of the sugar, **digitoxose** (a modified aldohexose,  $C_6H_{12}O_4$ ) and a non-sugar component **digitoxigenin**,  $C_{23}H_{34}O_4$ . The latter substance is known as a **genin** or **aglucone**. A dozen or so different aglucones have been obtained by the hydrolysis of a variety of physiologically active glycosides. In the plant tissues even more complicated glycosides occur for it has been shown that digitoxin itself is the product of a hydrolytic reaction which occurs during isolation, a molecule of glucose and acetic acid being split off. The aglucones are less powerful drugs than the glycosides and much less soluble in water. The preparations used in medicine are mixtures of various glycosides.

The aglucones derived from the **cardiac glycosides** all contain the cyclopentenophenanthrene nucleus. All four rings are non-aromatic. The hydroxyl group in position 3 so characteristic of the sterols and sex hormones is also present in all but one instance, as are the methyl groups in positions 13 and 10 (in one instance an aldehydo group  $-CHO$  replaces  $-CH_3$  at 10). The characteristic grouping of the cardiac aglucones seems to be an unsaturated lactone ring attached to position 17 and an hydroxyl group at 14.

**Toad Poisons.** In various species of toads the glands located behind the eyes secrete a poisonous material. This has long been known and the crude dried preparation has been used as a drug in China for centuries. The physiologically active compound occurs combined with an amino acid (Chap. XXXI). On hydrolysis, the non-nitrogenous compound is liberated. As in the case of the cardiac glycosides, the substance produced by hydrolysis is called a **genin**. Several such genins have been prepared in a pure state and their structure wholly or in part determined. The cyclopentenophenanthrene skeleton has been shown to be present, all four rings being non-aromatic. Like the heart poisons, an unsaturated lactone is attached to carbon atom 17 and one or more hydroxyl groups are present at different points in the molecule; positions

10 and 13 each carry methyl groups, at least in the one genin whose structure has been most carefully determined. In short, except for the side chain, the characteristic features of the sterol molecule are repeated.

**Saponins.** Certain substances which occur fairly widely distributed in plants have the property of forming a type of colloidal solution in water which foams on shaking like a soap solution. These materials are known as saponins. A few of them find limited uses in medicine and industry as foam producers. They are not a closely related group of compounds either biologically or chemically but the striking characteristic of their aqueous solutions has resulted in a diversity of compounds being classed together. They are all glycosides and on hydrolysis the non-sugar component (called a *sapogenin*) may be isolated.

Three sapogenins which may be prepared from the saponins extracted from the plants of the digitalis family are of special interest as they have been found to be related to the sterols. Their structures contain the usual cholesterol skeleton (including the two methyl groups at positions 10 and 13 and an hydroxyl group at 3). The side chain contains seven carbon atoms with cyclic ether linkages involving two oxygen atoms. All rings are completely saturated. Since saponins from at least two other families of plants besides the digitalis have yielded the same or similar genins, this type of structure is apparently not confined to one genus. The saponin (*i.e.*, glycoside) **digitonin** (from digitalis) has the rather remarkable ability to form a sparingly soluble molecular compound with cholesterol. A number of other sterols having in position 3 a free hydroxyl group with the same stereochemical configuration as cholesterol are also precipitated as stable molecular compounds with digitonin. This reaction has been very useful in isolating and characterizing sterols. Probably closely related to this affinity for cholesterol is the fact that digitonin and related saponins have a powerful hemolytic action, that is, they break the membrane of the red blood cells, probably by combining with cholesterol or similar substances in the membrane.

Another group of sapogenins are more closely related to the sesquiterpenes (p. 492). On selenium dehydrogenation they yield 1, 2, 5-trimethylnaphthalene. They contain thirty carbon atoms, thrice the number present in the terpenes and hence are designated as triterpenes. Certain acids of plant origin appear to belong to this same class of substances.

**Rosin.** The residue left behind in the manufacture of turpentine by distillation (p. 187) is a solid known as rosin or colophony. It is a mixture of **abietic acid**,  $C_{19}H_{29}COOH$ , and its anhydride. Abietic acid contains a carboxyl group attached to a partially hydrogenated phenanthrene nucleus which carries a methyl and isopropyl group. It is thus very distinctly related to the sterols on the one hand, and, because the molecule can be divided up into four isoprene residues (p. 491), to the terpenes on the other. Since abietic acid has a high molecular weight, its sodium and potassium salts have soap-like properties, and it is frequently used in connection with the manufacture of soap. It is also used in the manufacture of varnishes and, with alum, it is employed as sizing for paper.

**Biogenesis of Alicyclic Compounds.** We have seen (p. 491) that with the simple alicyclic compounds which occur in nature there appears to be a definite pattern in the structure corresponding to the isoprene residue. It is tempting to find similar patterns involving the isoprene chain in the sterols and related compounds; the characteristic methyl groups in positions 10 and 13 particularly tempt one to speculate that they correspond to the branched methyl group of isoprene. The side chain of cholesterol corresponds to two isoprene units with two of the carbon atoms of one unit involved in ring D. Various schemes can be devised by which isoprene units *might* be involved in the rest of the cholesterol skeleton if *ad hoc* hypotheses are made concerning the removal of additional carbon atoms by oxidation or the participation of three or six carbon chains (from sugars, perhaps) in the synthesis. At the present state of our knowledge such speculation is not too profitable. It is not even clear how the bile acids or the sex hormones are produced in animals. It only seems evident that both animal and plant cells readily produce certain general types of compounds and that the sterol structure is one of these types. Relatively slight modifications of this general pattern produce substances of very different physiological action which perform a variety of functions in the life of plants and animals.

#### QUESTIONS AND PROBLEMS

1. Define and illustrate the following terms: sterols, terpenes, hormones, sesquiterpene, vitamins, saponins, aglucones, sapogenins, bile acids.
2. What reactions (if any) would you expect when the following substances are treated with: (a) a dilute carbon tetrachloride solution of bromine; (b) methylmagnesium iodide in ether solution; (c) maleic anhydride and heat: vitamin D<sub>2</sub>, dipentene, menthol, cholesterol, the ester of cholic acid, the ester of cholanic acid.
3. With the aid of structural formulas show the relationship of the terpenes to isoprene. What portion of the cholesterol molecule appears to contain a grouping of atoms related to isoprene? Illustrate.
4. With the aid of diagrams representing a three-dimensional model, explain the isomerism of cholanic and allo-cholanic acid. How do you account for the fact that on catalytic hydrogenation at 200° cholesterol yields four stereoisomeric sterols, C<sub>27</sub>H<sub>47</sub>OH (one, coprosterol, only in traces). When the hydroxyl group of each is replaced by hydrogen how many stereoisomeric hydrocarbons, C<sub>27</sub>H<sub>47</sub>, would you expect? How are these hydrocarbons related to cholanic and allocholanic acids?
5. Devise a method for: (a) replacing the hydroxyl group of a sterol by hydrogen; (b) protecting the hydroxyl group during oxidation of the molecule

at another point; (c) proving the hydroxyl group was that of a secondary alcohol.

6. The hydroxyl group of lithocholic acid,  $C_{24}H_{40}O_3$ , is in position three. Write the structural formula. On dehydration and catalytic hydrogenation what product or products would you expect to obtain? On dehydrogenation of the secondary alcohol group and hydrogenation to regenerate this group how many isomers would you expect to obtain?

7. Make a list of the substances of biological interest which have been mentioned which contain the perhydrocyclopentanophenanthrene nucleus and carry an hydroxyl group at position 3. Which of these substances would you expect to be soluble in dilute alkali even if any carboxyl groups in the molecule were esterified? Explain.

8. Show all the steps in the degradation of the side chain in cholanic acid by the method which employs phenylmagnesium bromide. What fragments would be expected at each step to show the structure of the chain?

9. With the aid of structural formulas outline at least two transformations of the bile acids which indicate the presence of a reduced phenanthrene skeleton in their structure.

10. Write structural formulas for progesterone, vitamin  $D_3$ , the basic skeleton structure of the sapogenins of the digitalis family, camphor, the common skeleton of the toad poisons, testosterone.

11. What important natural substances containing the cyclopenteno-phenanthrene skeleton contain an aromatic ring? If the precursors of these substances in nature had a type of structure similar to that met with in cholesterol, what changes must have occurred in the formation of this ring?

## CHAPTER XXVIII

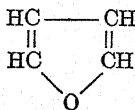
### HETEROCYCLIC COMPOUNDS

Cyclic compounds which contain two or more different elements in the ring are known as heterocyclic compounds. The elements which are commonly found together with carbon in ring systems are oxygen, sulfur, and nitrogen. We have already encountered a number of heterocyclic compounds in connection with our study of aliphatic chemistry. For example, lactones, cyclic anhydrides, cyclic imides, and the cyclic forms of the sugars are all heterocyclic compounds. Such substances, which are closely related to the aliphatic compounds, are usually considered in connection with aliphatic chemistry and require no separate treatment. There are, however, a certain number of heterocyclic compounds which have a peculiar degree of unsaturation, and thus resemble the aromatic hydrocarbons in their properties. They are sometimes referred to as aromatic heterocyclic compounds. The first part of the present chapter will be devoted to an elementary survey of some of the more important representatives of this type of heterocyclic compound. A great many drugs and other substances of biochemical interest are derivatives of heterocyclic compounds. We shall consider some of these substances in the following two chapters.

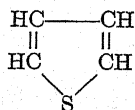
#### AROMATIC HETEROCYCLIC COMPOUNDS

The commoner heterocyclic compounds are derivatives of the following substances, each of which is to be regarded as the simplest representative of a large class:

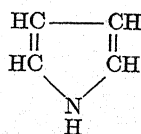
(a) *Five-membered rings:*



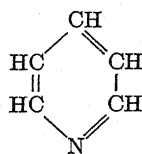
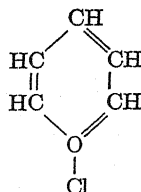
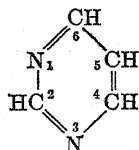
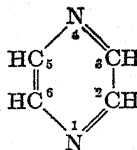
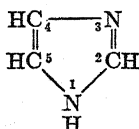
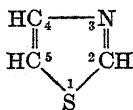
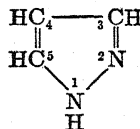
furan  
b.p. 32°



thiophene  
b.p. 84°  
508

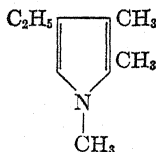


pyrrole  
b.p. 130°

(b) *Six-membered rings:*pyridine  
b.p. 115.5pyrylium chloride  
(a salt)(c) *Five- and six-membered rings with more than one atom other than carbon:*pyrimidine  
b.p. 124°pyrazine  
b.p. 115°imidazole  
b.p. 255°thiazole  
b.p. 117°pyrazole  
b.p. 187°

The position of substituents is indicated in the case of the systems of class (a) and (b) by numbering the ring starting with the nitrogen, oxygen, or sulfur atom and proceeding counter-clockwise (as the formulas are usually written). Another method is to designate the atoms on both sides of the ring immediately adjacent to the "hetero-atom" as  $\alpha$ , the next  $\beta$ , and in the six-membered ring, the atom at the opposite end as  $\gamma$ . The numbering of the rings in the system of class (c) is shown in the formulas themselves. Substituents on nitrogen are usually designated by the letter N before the substituent. Thus N-methyl-2,3-dimethyl-4-ethyl pyrrole or N-methyl- $\alpha,\beta$ -dimethyl- $\beta'$ -ethyl pyrrole has

the formula:



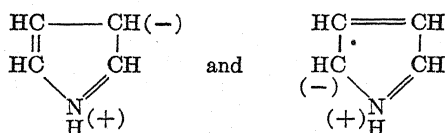
An outline formula with the double bonds written in, is often employed in representing the structure of heterocyclic compounds.

It will be noted that the compounds in group (c) may be regarded as derived from those in groups (a) and (b) by substitution of  $\text{—N=}$  for a CH group. All the possibilities are clearly not exhausted by the above list and other types of aromatic heterocyclic compounds containing oxygen, sulfur, and nitrogen are known. The five-membered rings containing two nitrogen atoms are known as the azoles, the six-membered rings as the azines. Instead of the trivial names listed above the structure may be indicated by numbers thus: pyrimidine is 1, 3-diazine, pyrazine is 1, 4-diazine.

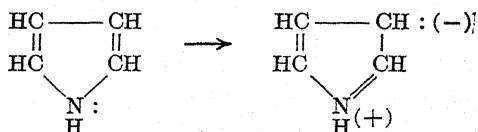
**Position of the Double Linkages.** For all the compounds listed in groups (a), (b), and (c), it is possible to write at least one other structure without shifting an atom or group. This is most clearly seen in the case of the six-membered rings where the situation in this respect is identical with that in benzene. If the pyridine ring is made unsymmetrical, for example, by the introduction of a substituent on the atom adjacent to nitrogen, two isomeric arrangements of the linkages may be written. In pyrimidine, which is in itself unsymmetrical, two formulas are conceivable, one with the linkage  $\overset{6}{\text{—CH}}=\overset{1}{\text{N}}-\overset{2}{\text{CH}}=\overset{3}{\text{N}}-\text{}$  as shown, the other having the linkage  $\overset{6}{\text{—CH}}-\overset{1}{\text{N}}=\overset{2}{\text{CH}}-\overset{3}{\text{N}}=\text{}$ . Isomers corresponding to such formulas have never been found. Instead, we find that the substance has a pronounced stability compared to open chain compounds or ring systems where such possibility of shifting bonds does not occur. This is due to the phenomenon of *resonance* already discussed in connection with guanidinium salts (p. 258) and benzene (p. 329).

With the five-membered rings the alternative structures involve the assumption that a negative charge may be localized on a carbon atom while the oxygen, nitrogen, or sulfur is positive. (Compare the structure of the amine oxides (p. 167) and isonitriles

(p. 168). For example, pyrrole could have the following structures:



A free pair of electrons is located on the atom marked CH(−) while the electrons about the nitrogen atom are arranged as in an ammonium ion. The electron shift from the structure shown by the usual formula to that shown in the formula to the left above is as follows:



This shift should be compared with that involved in the resonance of guanidine (free base) and the full electronic formulation given on p. 260 should be consulted. Isomers of this type have never been isolated. The compound in question has increased stability due to resonance between these structures and the one represented by the usual formula.

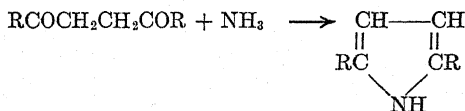
The increased stability, due to resonance, of such five-membered heterocyclic compounds as furan, thiophene, and pyrrole is probably less than in the case of the six-membered rings but is still very pronounced.

**Reduced Heterocyclic Compounds.** A great variety of heterocyclic compounds are known which may be regarded as partial or complete hydrogenation products of the substances just considered. They correspond to the alicyclic compounds. It will be evident that the addition of two or more hydrogen atoms to any of the systems we have so far considered will yield a substance with one or more CH<sub>2</sub> groups. A great variety of such compounds and their derivatives are known. Since many of them (*e.g.*, lactones, cyclic ethers, and anhydrides) are derived from open chain compounds, they are usually considered in connection with aliphatic chemistry. When such substances differ from the heterocyclic aromatic compounds by only one pair of hydrogen atoms, they

are often easily dehydrogenated as we have seen to be the case with alicyclic compounds (p. 484).

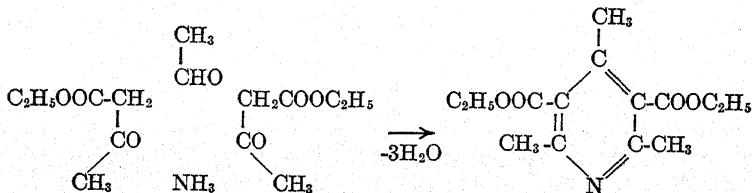
**Methods of Preparation.** Heterocyclic compounds are prepared either by condensation reactions which lead to ring formation or by transformations of readily accessible substances which contain the heterocyclic ring in question. Thus a number of simple furan derivatives may be prepared from the furan aldehyde, **furfural** (p. 303), which is in turn easily formed from the pentoses. By distilling bran, corncobs, or similar material with dilute acids, furfural is formed. It is prepared industrially from oat hulls and corncobs.

Unlike furan, there is no simple derivative of pyrrole available from which other derivatives may be prepared. Pyrroles are, therefore, made by methods involving ring closure. As an example, the formation of pyrroles by heating 1, 4-diketones with ammonia may be mentioned:



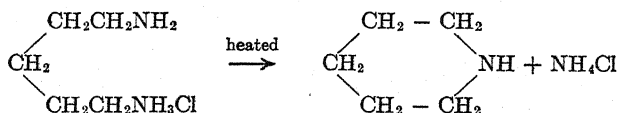
Substituted furans may also be made from 1, 4-diketones by heating with dehydrating agents. It is believed that this reaction proceeds by the elimination of water from the dienol of the diketone.

**Substituted pyridines** are formed when  $\beta$ -ketoic esters, an aldehyde, and ammonia are allowed to interact. This reaction may be indicated by the use of acetaldehyde and acetoacetic ester. It illustrates the fact that several molecules may interact in what appears to be an extremely improbable manner in order to produce a relatively stable, heterocyclic, aromatic compound:



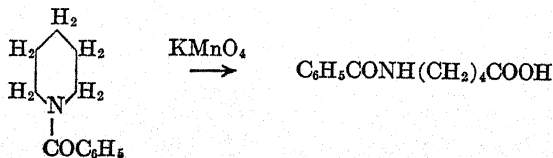
The resulting diester on saponification yields a dibasic acid which readily loses carbon dioxide, yielding 2, 4, 6-trimethylpyridine.

The synthesis of more highly reduced compounds may be illustrated by considering the completely hydrogenated pyridine,  $C_5H_{11}N$ , **piperidine**. This compound may be synthesized either by reducing pyridine with sodium and ethyl alcohol or by heating an open chain diamine:

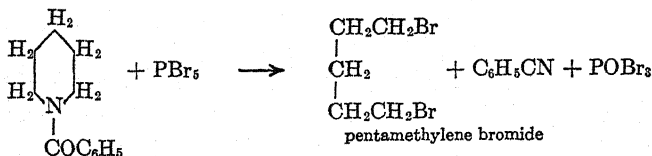


Since pyridine occurs in coal tar, from which it is isolated commercially, it may be used as a starting point in the synthesis of a number of derivatives. Like benzene it may be sulfonated and nitrated but with greater difficulty. Though the analogy with benzene is in this case striking, it cannot be pressed too far, particularly in the case of such five-membered rings as pyrrole. Indeed, as far as specific reactions are concerned each one of the ring systems listed on p. 509 has a chemistry of its own just as does benzene, naphthalene, and anthracene.

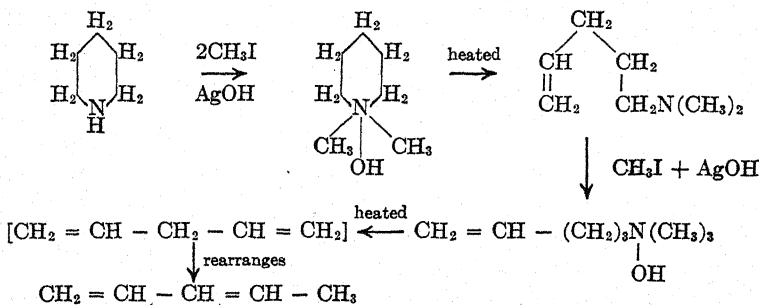
**Opening Heterocyclic Rings.** For the purpose of determining structure, it is important to be able to transform cyclic compounds into open chain derivatives. In general, the aromatic heterocyclic compounds and their reduction products contain rings which are opened with difficulty. (The lactones and cyclic imides, amides, and anhydrides form an exception to this rule.) Vigorous oxidizing agents will usually cleave the ring with the resulting formation of dibasic acids. For example, the N-benzoyl derivative of piperidine (prepared by treating piperidine with benzoyl chloride and sodium hydroxide) is oxidized as follows:



Treatment of N-benzoyl piperidine with phosphorus pentabromide also results in ring cleavage thus:



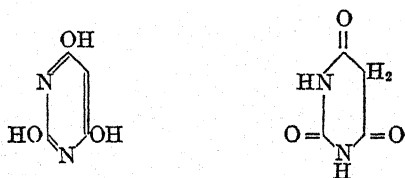
**Exhaustive Methylation.** A very important method of opening nitrogen-containing rings which has been much employed in determining the structure of alkaloids (p. 531) depends on the thermal decomposition of quaternary ammonium bases (p. 167). An application of this reaction to piperidine is as follows:



**Basic and Acid Properties.** Pyrrole and its derivatives are both extremely weak acids and extremely weak bases. In aqueous solution neither property is evident, as the salts are completely hydrolyzed. Only in non-aqueous solvents may the hydrogen of the NH group be replaced by such a metal as potassium. When pyrrole and potassium hydroxide are heated in the absence of water, for example, the potassium derivative is formed. Like the amides, and unlike the amines, the tendency for the nitrogen of pyrrole to pass into the ammonium form is very slight. On the other hand, the reduction product of pyrrole, pyrrolidine  $\text{C}_4\text{H}_9\text{N}$ , has the basic strength of an ordinary secondary amine and has not any of the acidic properties of pyrrole. It is clear that the two double bonds in the pyrrole ring have much the same effect on the nitrogen atom as the presence of the carbonyl group in amides (see phthalimide, p. 427).

Pyridine is a weak base with a dissociation constant of the same order of magnitude as aniline (see diagram, p. 158). Its reduction product, piperidine, however, is comparable in strength to the aliphatic amines. The influence of the unsaturated linkage of the nitrogen atom is, therefore, enormous. Imidazole, thiazole, pyrazole, pyrimidine, and pyrazine are all weak bases. The NH group of imidazole also has extremely weak acid properties similar to those manifested by pyrrole.

The introduction of hydroxyl groups into the heterocyclic rings decreases the basicity of the molecule. When a number of such groups are present the compound is usually too weak a base to form salts which are stable in aqueous solution. This may be interpreted as an effect of the hydroxyl group on the heterocyclic aromatic ring or by supposing that the compounds exist largely (or entirely) in the tautomeric form. For example, it will be noted that barbituric acid (p. 251) (which is too weak a base to form salts with acids in aqueous solution) can also be regarded as a trihydroxypyrimidine. The tautomeric formulas written below, it will be noted, involve the shift of a hydrogen atom. They are not to be confused with the different arrangements of double bonds which appear to be possible in the true pyrimidine ring and represent the resonating structures. No tautomeric isomers have ever been isolated nor has any clear evidence of their existence been obtained. The situation is similar to that met with in the amides and cyanic acid (p. 253).

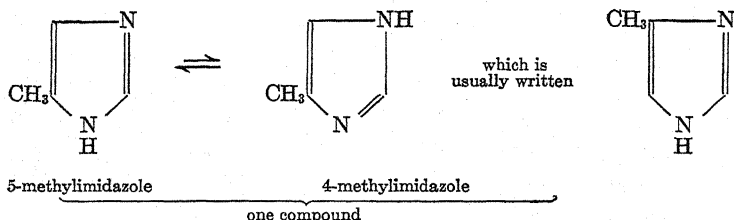


tautomeric forms of trihydroxypyrimidine  
(malonyl urea or barbituric acid)

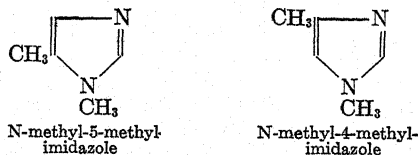
The acid properties of the hydroxy derivatives of heterocyclic compounds increase, as a rule, with the number of hydroxyl groups. If the formula with hydroxyl groups is correct, these compounds are analogous to phenols. They are stronger acids than simple phenols, however. Barbituric acid, for example, is comparable in strength to acetic acid.

Both tautomeric formulas of such compounds as barbituric acid correspond to systems with considerable resonance energy. The trihydroxy form contains a pyrimidine ring which can resonate as does the ring in benzene. The malonyl urea form would manifest the same type of resonance as urea (p. 260). It is impossible at present to conclude with assurance which of the two forms should be most stable in aqueous solution. Perhaps a very mobile equilibrium is present between the two tautomeric resonating systems.

**Tautomerism of Imidazole and Pyrazole.** The formulas of imidazole and pyrazole show that the rings in these compounds contain both a  $>NH$  and a  $=N-$  linkage. The interchange of hydrogen between the two nitrogen atoms in both types of rings is very rapid. If the ring in imidazole, for example, is made unsymmetrical by the introduction of a methyl group, two isomers might be expected according to whether the group is adjacent to the  $>NH$  or  $=N-$ . Such isomers have never been isolated. We are dealing here as in the case of cyanic acid with two tautomeric forms.

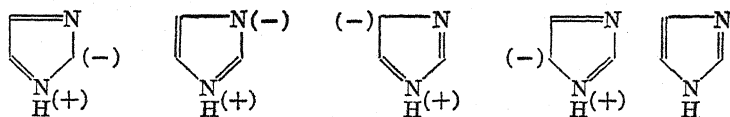


For this reason the 4 and 5 positions are identical in the imidazole ring. Similarly the 3 and 5 positions are identical in pyrazole. If, however, the hydrogen atom on nitrogen is replaced by a methyl group, a tautomeric shift is no longer possible and the following isomers, for example, can be readily obtained:



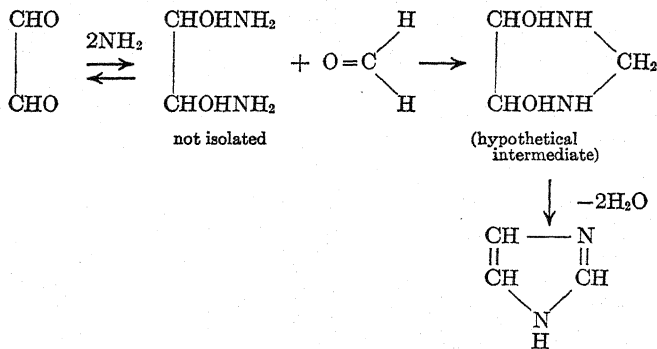
*It is important to distinguish the tautomeric shift in the imidazole and pyrazole rings from the resonance of these rings. The resonating*

structures are identical in the position of all the atoms, and differ only in the location of the valency electrons (see formulas for resonating structures of pyrrole, p. 511); the tautomeric structures differ in the position of a hydrogen atom.



resonating structures of imidazole

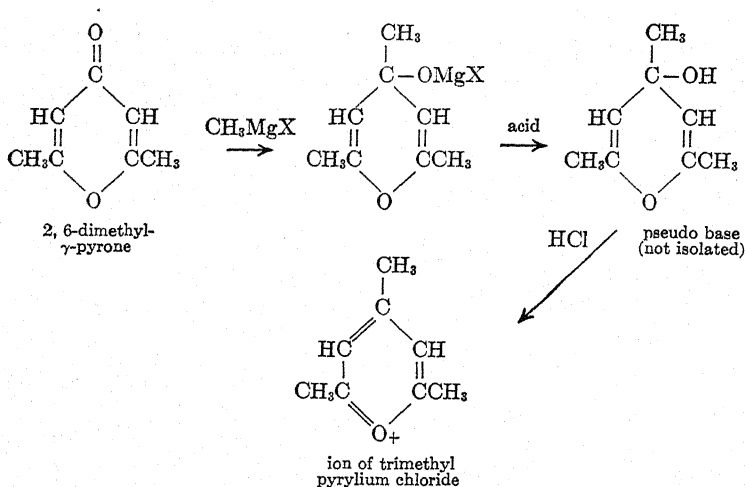
**Synthesis of Imidazole.** Imidazole can be readily synthesized from glyoxal (p. 193) and hence is known as **glyoxaline**. The steps in the reaction, when glyoxal, formaldehyde, and ammonia are allowed to react, are probably as follows:



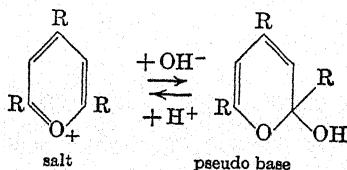
**Pyrones and Pirylium Salts.** The six-membered ring containing one oxygen atom requires a few words of special mention. Since oxygen normally has a valence of 2, unlike nitrogen it can not replace a  $-\text{CH}=\text{}$  group in an aromatic six-membered ring. In non-aqueous solution, ethers ( $\text{ROR}$ ) can form salts with acids, oxygen becoming formally quadrivalent but actually having only three atoms or groups attached by covalent bonds:  $\left[ \begin{array}{c} \text{H} \\ \vdots \\ \text{R} \ddot{\text{O}} \text{R} \end{array} \right]^+ \text{Cl}^-$  (p. 168). It is clear that an oxygen atom in such a condition could replace a  $-\text{CH}=\text{}$  group of a benzene ring. This is the case in the pyrylium salts which contain the structure already formu-

lated (p. 509). It is of great interest that although the basic properties of oxygen in the usual types of compounds (*i.e.*, ethers, ketones, etc.) are so weak that they are not manifested in dilute aqueous solution, the pyrylium salts are stable in water. This is a striking illustration of the relative stability of an aromatic ring and may be explained nicely in terms of resonance.

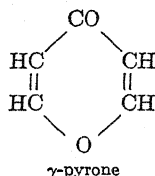
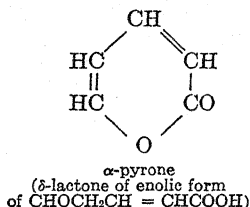
Pyrylium salts without substituent groups are unknown. Trimethylpyrylium chloride may be prepared from 2, 6-dimethyl- $\gamma$ -pyrone by the following reactions.



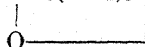
When treated with alkali, pyrylium salts are converted into compounds with an hydroxyl group in the  $\alpha$  or  $\gamma$  position known as **pseudo bases**. On treatment with acid, the pseudo bases form pyrylium salts. The reaction has been studied most extensively with the triaryl pyrylium salts, for example, triphenyl pyrylium chloride. A pseudo base is an intermediate in the synthesis of trimethyl pyrylium chloride given above.



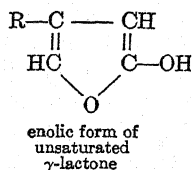
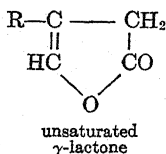
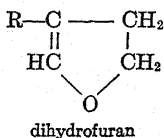
The pyrones in which the keto group and oxygen bridge are opposite are known as  $\gamma$ -pyrones; those in which the CO group is adjacent to the oxygen are called  $\alpha$ -pyrones. An inspection of the formula of  $\alpha$ -pyrone (below) shows that it is the  $\delta$ -lactone of an unsaturated acid.



**Lactones.** The usual lactones containing five- and six-membered rings are formally related to reduced furan and pyrylium compounds respectively. Thus, a  $\delta$ -lactone  $\text{CH}_2(\text{CH}_2)_3\text{CO}$  may



be regarded as a keto (or oxo) derivative of a hexahydropyrylium salt, or as tetrahydro  $\alpha$ -pyrone. A  $\gamma$ -lactone, in turn, may be regarded as an  $\alpha$ -keto derivative of tetrahydro furan. An unsaturated  $\gamma$ -lactone, being a derivative of dihydro furan, is in its enolic form a phenol of the furan series. (Such a grouping is characteristic of the cardiac aglucones, p. 504.)



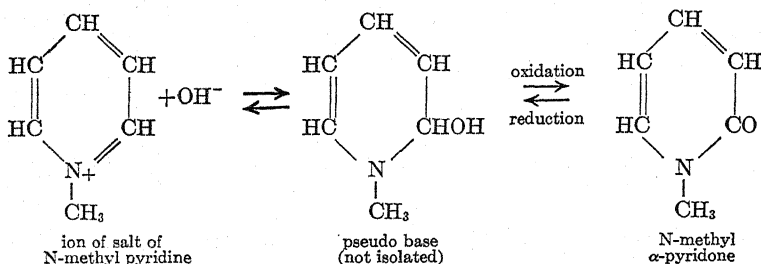
It should be carefully noted that the lactone ring (saturated or unsaturated), unlike almost all other heterocyclic rings, is easily opened by hydrolytic agents.

**Pyridinium Compounds.** Pyridine, being a tertiary amine, can add one mole

of an alkyl halide forming a quaternary ammonium salt,  $\text{C}_5\text{H}_5\text{N}^+\begin{matrix} \text{CH}_3 \\ | \\ \text{I} \end{matrix}$ . The

ion of this salt represents still another type of aromatic ring analogous to pyridine on the one hand and the pyrylium salts on the other; the heterocyclic atom (nitrogen) carries a positive charge. On treating the aqueous solution

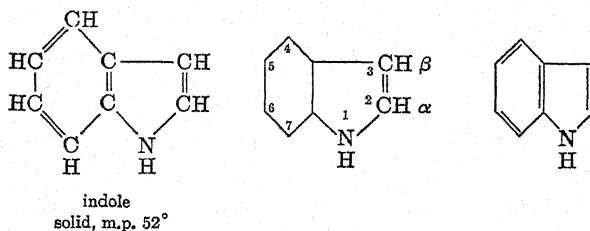
of the iodide with silver hydroxide, the quaternary base is formed. This is a strong base (compare tetramethyl ammonium hydroxide). Since the compound is easily oxidized by potassium ferrieyanide to N-methyl- $\alpha$ -pyridone, it is probable that some pseudo base is in equilibrium with the free base.



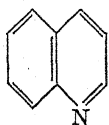
The only difference between the pyrylium salts and N-alkyl pyridinium salts, so far as this reaction is concerned, is in the relative stability of the pseudo base in alkaline solutions. Depending largely on the solubility of the pseudo base, the heterocyclic compounds which carry a positive charge on the hetero atom behave, when treated with alkali, either like N-alkyl pyridinium salts or like pyrylium salts.

### CONDENSED BENZENE AND HETEROCYCLIC RING SYSTEMS

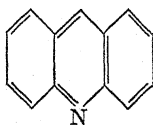
Many types of compounds are known in which a heterocyclic ring is fused to one or more benzene rings. The simplest and one of the most important representatives of this large class of substances is **indole**, a product of decomposition of certain proteins. To illustrate the conventions employed in writing the structural formulas of this substance, three methods of writing the formula of indole are given below:



The nomenclature of substituents is indicated by the numbering of the central formula.

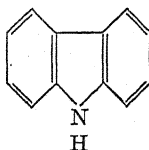
*Some Representative Condensed Heterocyclic Compounds*

quinoline  
b.p. 239°



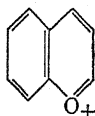
acridine  
solid, m.p. 110°

weak bases like pyridine

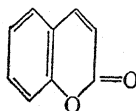


carbazole  
m.p. 238°

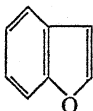
no basic properties  
in aqueous solution



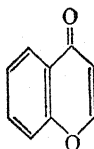
ion of benzo-  
pyrylium salts



coumarin (a lactone)  
(See p. 408)



coumarone (benzofuran)  
b.p. 170°

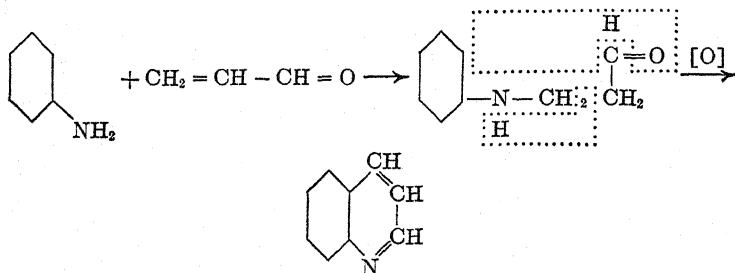


chromone

In their chemical reactions these condensed systems for the most part show the characteristic reactions of both the benzene and the heterocyclic ring. Except for the lactone, coumarin, the heterocyclic ring is remarkably stable. In quinoline and acridine the properties of the six-membered rings are modified by the pyridine nucleus to which they are fused. Thus, like naphthalene and anthracene, these substances deviate to some extent in their behavior from the reactions characteristic of the monocyclic compounds.

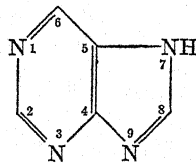
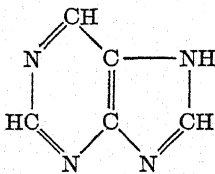
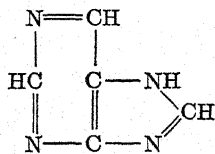
**Synthesis of Quinoline.** To illustrate the use of condensation reactions in synthesizing condensed heterocyclic compounds, the Skraup synthesis of quinoline may be given. This consists in heating a mixture of aniline and glycerol with strong sulfuric acid and an oxidizing agent such as arsenic acid. Acrolein (p. 289) is probably formed as the first product, which then condenses with

aniline (1, 4 addition) and under the influence of the oxidizing agent closes the heterocyclic ring.



### PURINES

Many compounds are known in which two or more heterocyclic rings are fused together. This type of structure is found in a number of substances produced in nature. One or two important classes of substances of interest to the biochemist contain the purine system, which is composed of a pyrimidine ring and an imidazole ring fused together. The structural formula for the parent substance is written below according to three different conventions. At first sight the reader may have difficulty in recognizing the identity of these formulations. The one on the extreme left in which a six-membered ring is written in the form of a rec-



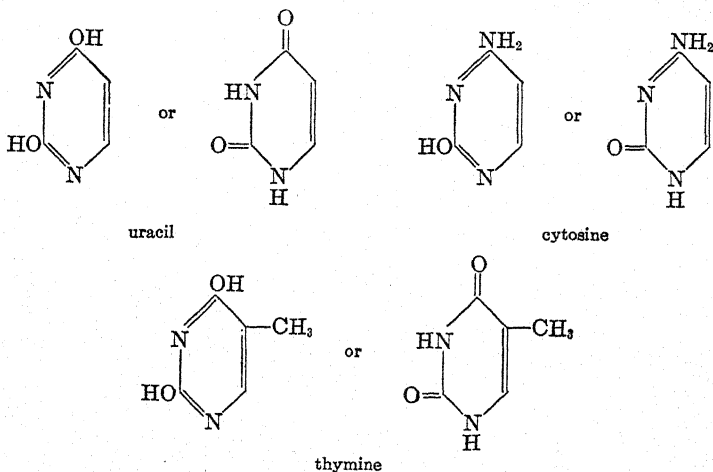
Three ways of writing the structural formulas of purine.

tangle has been employed by almost all chemists for many years. The use of this convention tends to obscure the relationship of the purines to other aromatic, heterocyclic compounds. In recent years an increasing number of chemists have employed such formulas as that shown on the extreme right. The reader should master both methods in order to be able to read rapidly in the biochemical literature.

**Nucleic Acids.** Very complex acids containing phosphorus occur widely distributed in plant and animal cells; they are known as the nucleic acids. They often occur together with certain proteins (Chap. XXXI), either as salts or perhaps joined by an amide linkage. Such combinations of nucleic acid and proteins have been designated as the **nucleoproteins**; they occur in particularly large amounts in the thymus and pancreatic glands of animals. A somewhat different nucleic acid is present in plant cells and is readily prepared from yeast. The nucleoproteins are believed to be important constituents of the nuclei of both plant and animal cells although their physiological function is not understood.

On hydrolysis, the nucleic acids yield phosphoric acid ( $\text{H}_3\text{PO}_4$ ), a molecule of a pentose, and five heterocyclic nitrogen compounds: cytosine, uracil, thymine, guanine, and adenine. The first three substances are derivatives of pyrimidine, the last two of purine.

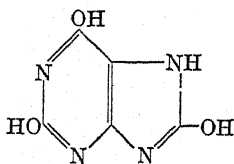
**Pyrimidines from Nucleic Acid.** The structural formulas of the three pyrimidines obtained by hydrolyzing nucleic acid are given below in the two possible tautomeric forms (see the discussion of barbituric acid, p. 515):



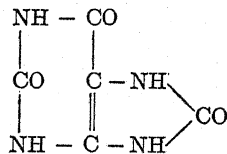
Since these hydroxy pyrimidines contain the grouping  $=\text{N}-\text{COH}=\text{N}-$  or  $\text{NHCONH}$ , they may be thought of as cyclic derivatives of urea, and are sometimes called **cycleic ureides** (see p. 250).

**Uric Acid.** The nucleic acids, which probably occur in all living cells and which decompose in the course of the oxidation reactions necessary for life, and the purine constituents in certain mammals

including man are transformed largely into uric acid. Under ordinary conditions only very small quantities of uric acid are found in the urine and body fluids of the higher animals. Under certain pathological conditions, however, large quantities of uric acid are produced in man and are deposited as the sparingly soluble sodium salt. Such deposits occur in the joints and produce the unpleasant symptoms characteristic of gout. Urinary calculi which may form in the bladder also contain uric acid, and the acid was isolated from such material as long ago as 1776 by Scheele. The ammonium salt of uric acid is the chief constituent of the excrement of reptiles, birds, and insects.



uric acid,  
2, 6, 8-trihydroxypurine  
(also known as  
2, 6, 8-trioxypurine)

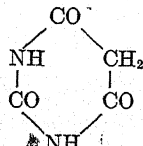


uric acid,  
Formula written to  
show ureide linkages

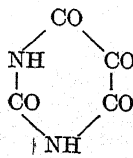
The two formulas written above for uric acid, represent not only two different conventions employed in writing the purine skeleton but two tautomeric possibilities. Tautomeric isomers of hydroxy purines have never been isolated. The situation is very similar to that encountered in the case of the hydroxy pyrimidines (see barbituric acid, p. 515).

Uric acid is a white, crystalline solid very slightly soluble in water. It is a weak, dibasic acid; the monosodium salt is difficultly soluble in water but the disodium salt is readily soluble. Uric acid has no basic properties.

**Structure of Uric Acid.** On oxidation uric acid is converted into alloxan and urea,  $\text{NH}_2\text{CONH}_2$ . Alloxan may also be made by the oxidation of barbituric acid (p. 251).

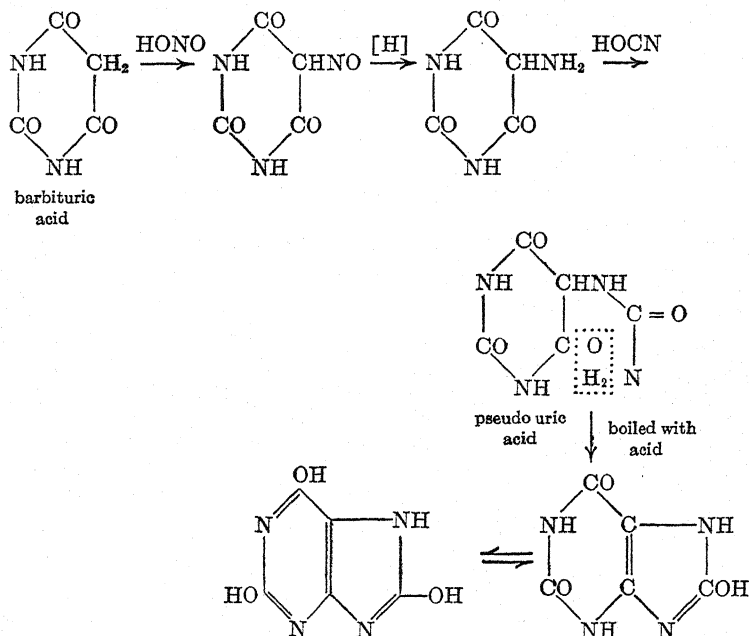


barbituric acid



alloxan

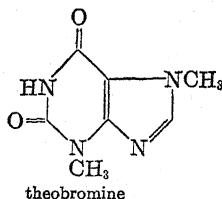
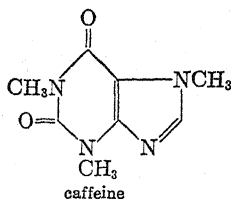
Since alloxan and urea are the oxidation products of uric acid, it is probable that the original molecule contained the skeleton of alloxan and, in addition, another ring containing a urea linkage. The proof of the structure of uric acid was finally accomplished by its synthesis by the following series of reactions:



The history of the investigation of the structure of uric acid covers almost the whole classical period of organic chemistry. The greatest knowledge of the subject is due to the work of Liebig and Wöhler over 100 years ago (1838). Baeyer in 1863 prepared pseudo uric acid (see above), but it was not till 1897 that Emil Fischer succeeded in finding the right conditions for converting this compound into uric acid itself. No other compound has had the honor of being the subject of investigation by four such masters of the science of organic chemistry.

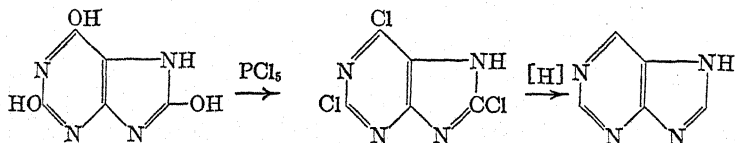
**Caffeine.** This is a close relative of uric acid which occurs in coffee and tea to the extent of a few per cent. Caffeine is used in medicine as a stimulant and diuretic. It crystallizes in water in silky needles which melt at  $237^{\circ}$ . It is only slightly soluble in water. It is a very weak base but forms characteristic salts with acids. It will be noted from its structure that it is related to uric acid by the substitution of 3 hydrogen atoms on nitrogen by methyl groups and the replacement of one hydroxyl group by hydrogen.

The weak basic properties in contrast to uric acid (which has no basic properties) are probably due to the fact that the imidazole ring carries no hydroxyl group. **Theobromine** is present in cocoa

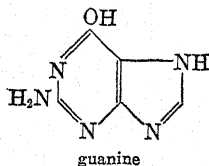
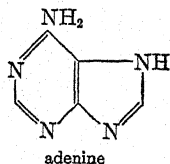


beans to the extent of a few per cent. It is a crystalline powder which melts at  $337^{\circ}$  and is only slightly soluble in water. It differs from caffeine in having only two methyl groups on the nitrogen atoms.

**Purine.** The parent substance of the purines can be prepared from uric acid by treating uric acid with phosphorus pentachloride, and reducing the trichloro compound thus formed with hydrogen iodide, followed by zinc:



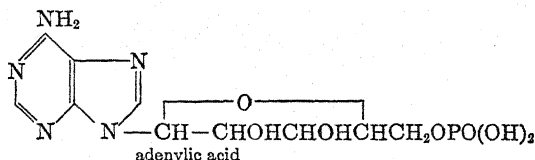
**Adenine and Guanine.** The two purine derivatives obtained by hydrolysis of nucleic acid have the following structures (or that of the tautomeric isomer):



In the nucleic acid from yeast each of the purine derivatives is combined in position 9 with a sugar, *d*-ribose (p. 303), which in turn carries a phosphate radical on the terminal atom. Such a combination of nitrogen compound, sugar, and phosphoric acid is called a **nucleotide**; the phosphorus-free glycoside is designated a **nucleoside**. In the nucleic acids four or more nucleotides are linked together, probably through oxygen atoms of the phosphate group. They are really polynucleotides.

An example of a mononucleotide is **adenylic acid**, which occurs in muscle

tissue (p. 315) both as such and combined with another molecule of phosphoric acid (adenylic acid pyrophosphate). This extra phosphate residue may be lost and gained reversibly under the action of enzymes.

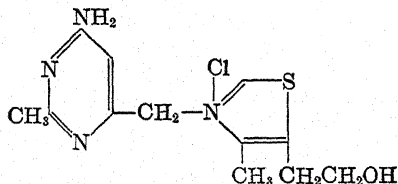


On alkaline hydrolysis, adenylic acid loses phosphoric acid and passes into the nucleoside adenosine. On acid hydrolysis, the glycoside linkage to nitrogen is cleaved and adenine is set free. The glycosidic linkage is apparently attached in the 9 position though it was formerly believed that the other nitrogen of the imidazole ring (position 7) was involved.

**Xanthine and Hypoxanthine.** In the animal body enzymes are present which bring about the de-amination (replacement of  $\text{NH}_2$  by  $\text{OH}$ ) of adenine and guanine (or their derivatives, such as adenylic acid). The corresponding mono- and dihydroxypurines are known as hypoxanthine and xanthine, respectively. They are weaker acids than uric acid, and since the imidazole ring carries no  $\text{OH}$  group, they show weak basic properties even in aqueous solution.

**Vitamin B<sub>1</sub> (Thiamin).** The substance originally called vitamin B has been shown by chemical and biochemical studies to be a complex of many substances. So far this complex has been resolved into the following crystalline compounds: B<sub>1</sub>, B<sub>2</sub>, nicotinic acid (pellagra preventing factor, p. 532), and B<sub>6</sub>. The latter (called also Adermin) when absent from the diet of rats, produces a peculiar dermatitis.

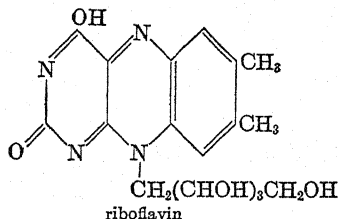
Vitamin B<sub>1</sub> is the **antineuritic vitamin**. It prevents beriberi in man and polyneuritis in animals. Its structure, which has been recently established by degradation and synthesis, is:



It will be seen that the substance is a quaternary ammonium salt of a substituted thiazole (p. 509); the group attached to the

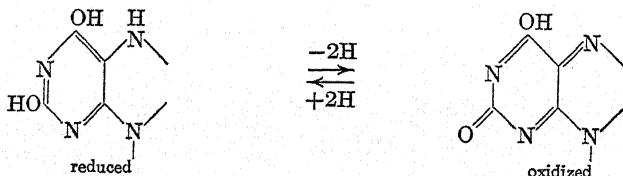
heterocyclic quaternary nitrogen atom contains a pyrimidine ring. The compound is isolated as a hydrochloride, one mole of HCl being bound by the amino pyrimidine nucleus. Vitamin B<sub>1</sub> is now manufactured by synthetic methods.

**Vitamin B<sub>2</sub> or Riboflavin.** This substance is sometimes known as vitamin G. It is a crystalline, orange-yellow solid which exhibits a characteristic green fluorescence in solutions. As we shall see, it is a component of a respiratory enzyme system present in living cells. It is essential for growth in chicks and rats. The elucidation of its structure and its synthesis have been accomplished recently.



The group attached to one of the two central nitrogen atoms is a reduced *d*-ribose molecule (ribityl). The ring system contains an oxy-pyrimidine and an ortho xylene ring fused on both sides of a 1, 4-diazine (p. 510).

**Respiratory Enzymes.** Intimately connected with the oxidation of food-stuff in the cells of the animal body are a series of enzymes (p. 590). One of these is a yellow substance, **flavoprotein**, which contains riboflavin linked to phosphoric acid (the primary alcohol group in the above formula is esterified by one OH group of phosphoric acid). This substance is in turn connected to a protein. The enzyme, flavoprotein, or riboflavin, or its phosphate is reversibly reduced and oxidized in a way reminiscent of the systems anthraquinone-anthrahydroquinone or indigo-leucoindigo (p. 461 and p. 558). Hydrogen is added reversibly at the middle =N- and =O group of the pyrimidine ring. In the process the left-hand ring probably undergoes the changes:



In the oxidation of certain substances in the cell, hydrogen is transferred from the substance being oxidized (the substrate) to this yellow pigment which is reduced. The reduced form then reacts with molecular oxygen yielding the colored oxidized form. The transfer of hydrogen from the substrate to the respiratory enzyme requires, however, at least one intermediary (a co-enzyme). This substance is a complex of adenylic acid and the riboside of the amide of pyridine-3-carboxylic acid (nicotinamide), the two glycosides being linked together through three phosphoric acid residues. (Pyridine-3-carboxylic acid is known as nicotinic acid because of its relation to nicotine, p. 532).

Other enzyme systems and other mechanisms are also involved in the oxidation of substances in the cell. One of these enzymes, **cytochrome**, contains iron and is related to hemoglobin (p. 607). It is also reversibly oxidized and reduced, but it seems to require for oxidation with free oxygen a co-enzyme which is the yellow respiratory pigment just described.

### QUESTIONS AND PROBLEMS

1. Write equations for the following reactions: Skraup synthesis of quinoline, the opening of the hexahydropyridine ring by exhaustive methylation, the preparation of 2, 4, 6-trimethylpyridine from aliphatic compounds.

2. Write structural formulas for: thiophene, 2, 3-dimethylfuran, N-ethyl pyrrole, 2-methylthiazole, 2-chloropyrimidine, 2, 4, 6-trihydroxypyrimidine, 2-hydroxypurine,  $\alpha$ -methylindole, acridine, xanthine.

3. Give the systematic names (indicating position of substituents by numbers) of the following: thymine, barbituric acid, piperidine, caffeine, cytosine, adenylic acid.

4. Outline the steps in the synthesis of the following compounds from urea and aliphatic compounds: alloxan, uric acid.

5. Which of the following substances do you think will combine with hydrochloric acid to form a salt in dilute aqueous solution? Which will react with dilute sodium hydroxide to form a salt? Theobromine, alloxan, 2, 3-dimethylpyrrole, tetrahydropyrrole, benzoylpiperidine, N-methylpiperidine, imidazole, 2-oxypyrimidine, uric acid.

6. Give two examples each of methods of closing a heterocyclic ring, of opening a heterocyclic ring, and of the transformation of one heterocyclic into another without opening the ring.

7. Write a general formula for a nucleotide. What reagent would you employ to prepare from such a substance: (a) a nucleoside; and (b) the heterocyclic compound?

8. Write the structural formula for 4-methyl-5-( $\beta$ -hydroxy-ethyl) thiazole. Given this substance and 2-methyl-5-cyano-6-amino pyrimidine, by what steps would you attempt to synthesize vitamin B<sub>1</sub>?

9. What is vitamin B<sub>2</sub>? How does it differ from the respiratory enzyme, flavoprotein? What reagents would you employ to bring about the reduction and oxidation of riboflavin in dilute, neutral, aqueous solution?

10. Define and illustrate the term pseudo base. From which of the following substances can pseudo bases be prepared and by what methods:

N-methylquinoline chloride, 2-methylpyridine chloride, 2-methylpyrimidine hydrochloride, 2, 4-dimethylpyrylium chloride, benzopyrylium bromide?

11. Discuss the tautomerism of barbituric acid. Write the formulas for the tautomeric forms of adenine.

12. Write a full electronic formula (showing all the valence electrons) for the three resonating structures of pyrrole.

13. When 5-methylimidazole is treated with an alkylating reagent which brings about the substitution of a hydrogen atom in a  $\text{>NH}$  group by an alkyl group, two isomers are obtained. What are their formulas and how do you explain their formation?

## CHAPTER XXIX

### NATURAL AND SYNTHETIC DRUGS

The *materia medica* of the medical profession a hundred years ago was based on the accumulation of generations of experience in regard to the physiological action of inorganic chemicals and natural drugs. The latter substances were particularly valuable, and have remained so to the present day. During the last sixty years these natural drugs have been supplemented, but not supplanted, by a number of synthetic products. Both the old and the new remedies are used by the modern physician.

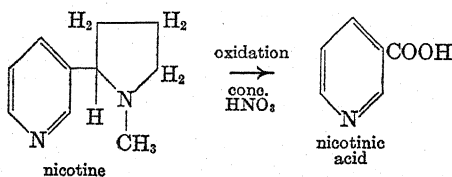
In tracing the modern history of drugs, we can distinguish two different aspects of the chemical development. On the one hand, we find that a multitude of new substances were prepared in the organic laboratory, and many of these proved to be valuable. Two examples will suffice — aspirin and phenacetin. On the other hand, we must note that many chemists soon turned their attention to the natural products themselves, isolated the essential ingredient, and struggled with the difficult problem of its structure. As a result of this work, the constitution of many of the natural drugs was slowly revealed. Although the commercial synthesis of most of the well-known natural drugs has not yet been accomplished, a knowledge of the structure of the natural products has led to the manufacture of related synthetic products which have proved to be of great value.

We have already considered a number of synthetic drugs which are produced from aromatic compounds; for example, aspirin and other derivatives of salicylic acid (p. 423). It only remains, therefore, to consider some of the natural drugs, and certain rather complicated products whose synthesis has been inspired by a knowledge of the action and structure of the natural substances.

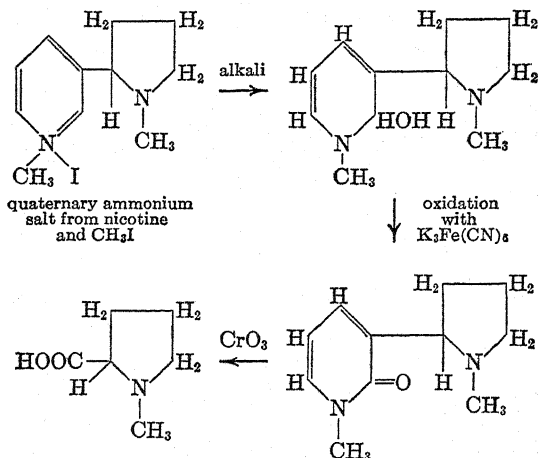
**Alkaloids.** The name alkaloid is usually restricted to a group of basic, nitrogenous plant products which have a marked physiological action. The majority of these are complex, heterocyclic

compounds. In recent years, certain bases isolated from animal tissues have been sometimes included in the alkaloids. The basic properties of the alkaloids are due to the presence of amino groups or trivalent nitrogen atoms which are part of a heterocyclic system. The plant alkaloids have a bitter taste and are almost all laevo-rotatory. They are extracted from the plants by using dilute acids in which they dissolve because of the formation of soluble salts. Their purification is often an elaborate process. They are usually sold in the form of the water-soluble chlorides or sulfates; the free alkaloids are for the most part crystalline solids which are only very slightly soluble in water.

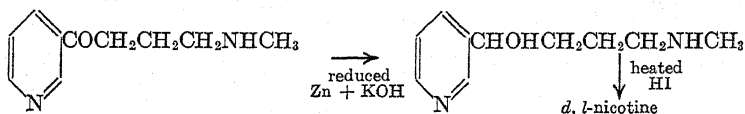
**Nicotine**, the alkaloid of tobacco, is one of the simplest of the group. It is also one of the few liquid alkaloids. The structural formula for nicotine is given below; it will be seen that in the molecule are two heterocyclic rings, one a pyridine ring, the other a completely hydrogenated pyrrole ring (pyrrolidine ring) with a methyl group attached to the nitrogen atom. On vigorous oxidation the five-membered ring is broken and the  $\beta$ -carboxylic acid of pyridine, **nicotinic acid**, is formed.



The structure of nicotine follows from two oxidative cleavages of the molecule. Direct oxidation with nitric acid (as given above) shows that the compound contains the pyridine ring with an attachment on the  $\beta$  carbon atom. If the quaternary ammonium salt is formed by adding methyl iodide to the pyridine ring (p. 519) the six-membered ring becomes sensitive to oxidation in alkaline solution because the pseudo base (p. 518) is easily oxidized to a ketonic group. The resulting compound no longer contains the resistant, aromatic, pyridine ring and on oxidation with chromic acid the six-membered ring is destroyed. The structure of the reduced pyrrole thus formed can be established by synthesis and the complete structure of nicotine follows:

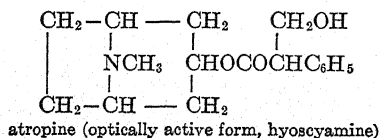


**Synthesis of Nicotine.** Nicotine has been synthesized by several methods. In one, an open chain, amino-keto derivative of pyridine is cyclized by the following reactions:

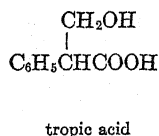
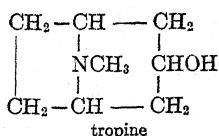


Natural nicotine is laevorotatory (the  $\beta$  carbon atom of the five-membered ring through which the pyridine nucleus is attached is asymmetric). The synthetic alkaloid is, of course, the racemic mixture. This can be separated by crystallizing the salts with an optically active acid as described in Chap. XII.

**Atropine.** The alkaloids present in the leaves and roots of *atropa belladonna* (deadly nightshade) and certain other plants are known as the belladonna alkaloids. The optically active *hyoscyamine* and the racemic form of the same compound, **atropine**, are isolated for use as drugs by oculists. These alkaloids dilate the pupil of the eye. Atropine has the following structure:



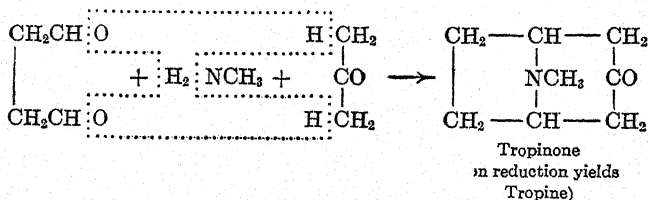
Atropine is the ester of a secondary alcohol, **tropine**, and an aromatic acid called **tropic acid**. The compound is easily decomposed into these compounds by hydrolysis



Tropine is optically inactive since it contains no center of asymmetry. Tropic acid, however, is obviously an asymmetric molecule, and the optical activity of hyoscyamine is due to this fact. Racemization occurs readily, and thus, the racemic alkaloid atropine is usually isolated.

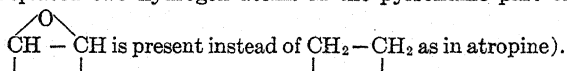
**Structure of Tropine.** The structure of tropine has been established by degradation and confirmed by synthesis. The presence of a secondary alcohol group follows from the ability to form esters and the fact that a ketone, **tropinone**, is formed on oxidation. On vigorous oxidation N-methyl succinimide (see p. 205) is formed; this fact establishes the left-hand part of the structure written above. As an intermediate a dibasic acid with the same number of carbon atoms as in tropine (seven) can be isolated. The ester of this acid on exhaustive methylation (p. 514) yields a doubly unsaturated dibasic acid,  $\text{C}_7\text{H}_8\text{O}_4$ , which on hydrogenation is transformed into the well-known aliphatic acid, pimelic acid (p. 196),  $(\text{CH}_2)_5(\text{COOH})_2$ . This series of transformations established the seven-membered carbon ring.

A very beautiful synthesis of tropine can be accomplished by allowing a mixture of succinic aldehyde, methyl amine, and acetone to interact in alkaline solution:



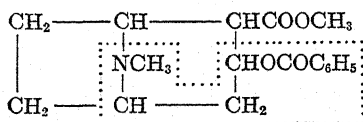
Better yields are obtained by employing acetone dicarboxylic acid (p. 215), the first product being a  $\beta, \beta'$ -dicarboxylic acid derivative of tropinone which on heating loses two molecules of carbon dioxide forming the ketone.

Scopolamine or hyoscine can also be isolated from the crude belladonna extracts. It finds some use in medicine because of its sedative and hypnotic action. It differs in structure from atropine in that one oxygen atom has replaced two hydrogen atoms in the pyrrolidine part of the molecule (*i.e.*,



**Cocaine.** One group of drugs is composed of those which act as *local anesthetics*. These substances when injected under the skin produce local insensibility to pain. For years the alkaloid cocaine was the only important drug of this type. It is extracted from the leaves of the *coca plant* which grows in the semi-tropics. (The coca plant should not be confused with the cocoa bean from which cocoa and chocolate are prepared.) Cocaine, like many alkaloids, is usually marketed as one of the salts (*e.g.*, the hydrochloride). The salts unlike the alkaloid itself are soluble in water.

Cocaine is closely related to tropine as the following structure shows. The grouping which appears to be primarily responsible for its specific physiological action is enclosed by a dotted line.

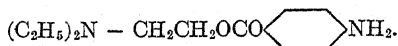


On hydrolysis the two ester linkages are readily broken, the products being methyl alcohol, benzoic acid, and an hydroxy acid differing from tropine only by a carboxyl group. The structure of this acid is easily established by transforming it into tropine. It can be synthesized by methods very similar to those employed for the synthesis of tropine.

Unlike tropine, this carboxylic acid is not symmetrical. There are therefore a number of different stereoisomers possible (eight in all). The synthesis usually produces two racemic mixtures. On resolution by the usual methods, one of these yields a laevorotatory compound which on benzylation and esterification with methyl alcohol produces the natural alkaloid cocaine. From the other pair of isomers *pseudo cocaine* can be prepared which is not very different in its physiological action from the natural alkaloid. This synthesis has been employed commercially. The industrial production of this rather complicated natural product is one of the striking feats of the synthetic chemist.

**Procaine.** A study of cocaine and other substances has led pharmacologists to the conviction that the grouping  $\text{>N}-\text{C}-\text{C}-\text{C}-\text{OCOC}_6\text{H}_5$  present in cocaine is largely responsible for its physiological action. (This grouping has been enclosed in dotted lines in the formula.) A number of new compounds have been synthesized which are simpler than cocaine and which contain this grouping or the similar one  $\text{>N}-\text{C}-\text{C}-\text{OCOC}_6\text{H}_5$ . These have been found to be local anesthetics of value and several have been put on the market.

The most successful synthetic local anesthetic is **procaine** (**novocaine**). This is used as the hydrochloride which is soluble in water; the free base has the following structure:



Except for the introduction of the para amino group and the shortening of the chain by one carbon atom, this compound has the same characteristic grouping that occurs in cocaine. The raw materials for the synthesis of procaine are para nitrobenzoic acid, ethylene chlorohydrin, and diethyl amine.

**Other Alkaloids.** In the table below are listed some of the alkaloids, including those previously discussed, which may be regarded as of particular interest. Caffeine and theobromine (pp. 525 and 526) may also be considered as alkaloids although their physiological action is comparatively slight.

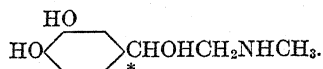
**Adrenaline and Ephredine.** These two substances are relatively simple natural bases which were formerly not classified as alkaloids, although they have a powerful and very important pharmacological action. Adrenaline is one of the active principles secreted into the blood stream by the *supra-renal glands* (see also p. 503). The production of this hormone in the animal organism has great physiological importance; its prime function appears to be to reinforce the action of the sympathetic nervous system.

The isolation of adrenaline from the supra-renal glands obtained from slaughtered animals provides the physician with one of his most valuable drugs. It is employed in very dilute solutions (0.1 to 0.01 per cent) and is administered by subcutaneous injection. It causes local contraction of the blood vessels and thus checks bleeding; for this reason it is used in surgery. It has also other uses in general medicine.

# SOME OF THE COMMON ALKALOIDS

NAME OF CLASS	TYPE OF RINGS CONTAINING NITROGEN	COMMON REPRESENTATIVES	SOURCE	PHYSIOLOGICAL ACTION
Conium alkaloids	Hexahydro-pyridine	Coniine	Hemlock herb	Very poisonous; paralysis of motor endings of nerves
Pepper alkaloids	Hexahydro-pyridine	Piperine	Pepper	Local irritant only
Tobacco alkaloids	Pyridine and tetrahydro-pyrrole	Nicotine	Tobacco	Very poisonous
Belladonna alkaloids	Tropine type	Atropine	Belladonna	Dilates pupil of the eye; very poisonous
Ergot alkaloids	Indole and reduced pyridine condensed	Ergotoxine	Certain fungi parasitic on rye	Contracts the uterus
Coca alkaloids	Tropine type	Cocaine	Coca leaves	Local anesthetic
Cinchona alkaloids	Quinoline + condensed reduced pyridine	Quinine	Bark of the cinchona tree	Specific for malaria
Opium alkaloids	Reduced pyridine condensed with reduced phenanthrene	Narcotine Morphine	Opium poppy	Narcotics
Strychnine alkaloids	Complex; complete structure still uncertain	Strychnine	Seeds of Nux Vomica	Very poisonous; in small doses increases blood pressure

The structure of adrenaline was established in 1905 by the synthesis of the racemic mixture and its subsequent resolution into the dextro and laevo forms. The latter proved to be identical with the natural drug. In the formula the asymmetric atom is shown by an asterisk.



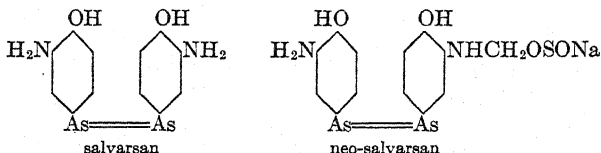
A comparison of the physiological activity of the dextro and laevo forms has shown that the latter is by far the more active. This is an illustration of the general principle mentioned in Chap. XII; although enantiomorphs are chemically identical, they usually differ in their relation to living things.

Adrenaline is now manufactured both by extraction from supra-renal glands and by synthesis. In the latter case the racemic mixture, of course, is formed; it is separated into the optical isomers. The substance is sold as the hydrochloride since it is more soluble in this form, and the solutions are more stable. Adrenaline itself is a white, crystalline substance which melts at 207°.

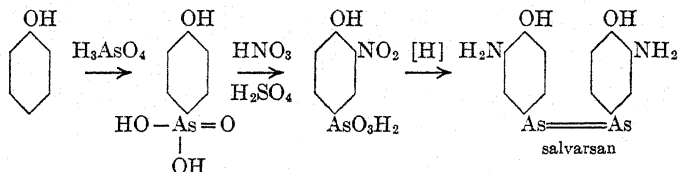
**Ephedrine**,  $\text{C}_6\text{H}_5\text{CHOHCH}(\text{CH}_3)\text{NHCH}_3$ , a very interesting plant product, finds rather wide use in medicine. This substance is closely related to adrenaline and resembles it in its pharmacological action. It is superior to adrenaline for many purposes because it can be taken by the mouth. Ephedrine is the active principle of a Chinese plant which for years has been used in China as a medicinal. Synthetic ephedrine is now manufactured in this country.

**Chemotherapy.** During the development of synthetic drugs it was hoped that a specific cure for each disease might be synthesized in the laboratory. This seemed possible particularly in the case of those diseases caused by bacteria and protozoa which could be isolated and studied *in vitro*. The aim of this work, called **chemotherapy**, was to prepare a compound which would be very poisonous to the invading organism but harmless to the host. In the early development of chemotherapy the most striking success was attained in the synthesis of two arsenical drugs extremely useful in combating syphilis — salvarsan (arsphenamine) and neosalvarsan. These were developed by Ehrlich; the first was

denoted as "606" by its discoverer because it was the 606th synthetic compound which he tried.



The synthesis of salvarsan from phenol is of some interest. Arsenic acid,  $\text{H}_3\text{AsO}_4$ , is closely related to hydrated nitric acid ( $\text{HNO}_3 + \text{H}_2\text{O} = \text{H}_2\text{NO}_4$ ), since arsenic and nitrogen occur in the same group in the periodic table. It is therefore not surprising that phenol may be arsenated by heating with arsenic acid. The product is analogous to nitrophenol but is hydrated. A nitro group is now introduced into the molecule in the usual way and the product reduced with sodium hydrosulfite ( $\text{Na}_2\text{S}_2\text{O}_4$ ). The nitro group is thus converted to an amino group and the arsenic acid group to the arsenic analog of the azo linkage. The steps are as follows:

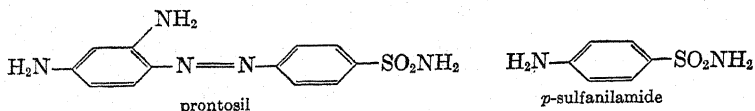


The salvarsan itself is isolated and sold as the dihydrochloride.

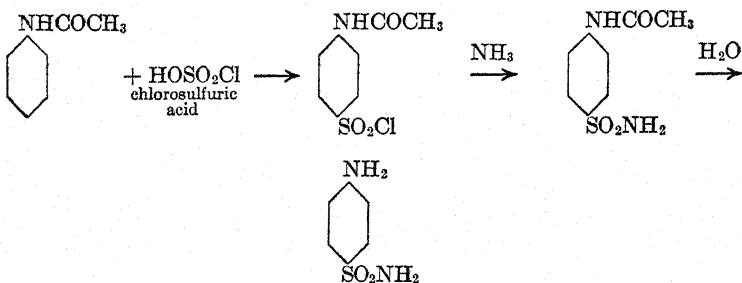
**Newer Developments in Chemotherapy.** Up to recent times the success of the application of chemotherapy to diseases has been limited to those infectious diseases caused by spirochetes (as in syphilis) and by protozoa. Today, there is scarcely a protozoal disease of man (sleeping sickness, malaria, amebic dysentery, leishmaniasis) which can not be cured by early treatment with the appropriate synthetic drug.

The search for chemical agents for control of such bacterial infections as streptococcal, staphylococcal, pneumococcal and others of this class was not rewarded until a few years ago. The first substance employed with striking success in treating certain coccal infections was a red dye known to the trade as **Prontosil**. It was made from sulfanilic acid (p. 367) and meta phenylene diamine (p. 376). On the basis of a long series of pharmacological investigations, it was determined that the portion of the prontosil molecule responsible for bactericidal action is para sulfanilamide which is the amide of *p*-sulfanilic acid (p. 367). Indeed, today this

latter, colorless substance is used in medicine in preference to the red azo dye.



Sulfanilamide is manufactured from acetanilide in the following manner:



It is interesting to note that very little, if any, sulfanilamide was manufactured during 1936, whereas over 267 thousand pounds were produced during 1937.

The discovery of the bactericidal activity of para sulfanilamide has revitalized research in this branch of chemotherapy. A very large number of derivatives of sulfanilamide have been synthesized and investigated. One of the most important of these derivatives is a pyridine derivative of sulfanilamide and it is called **sulfapyridine**. A pyridine nucleus is attached to the amide nitrogen atom of sulfanilamide through the beta position of the heterocyclic ring. This substance shows a more general action against various types of pneumococci than does sulfanilamide.

### QUESTIONS AND PROBLEMS

1. Ephedrine and adrenaline have similar pharmacological action. To what part of the molecule might one attribute this action?
2. Coniine has the empirical formula  $C_8H_{17}N$ ; on oxidation (dehydrogenation) with silver acetate, it yields a weakly basic compound, which on oxidation with chromic acid, produces pyridine- $\alpha$ -carboxylic acid. On exhaustive methylation and hydrogenation of the unsaturated hydrocarbon, coniine gives *n*-octane. What is its structure?
3. 2-Methylpyridine condenses with aldehydes to form unsaturated compounds. (The hydrogen atoms of the methyl group are equivalent in this

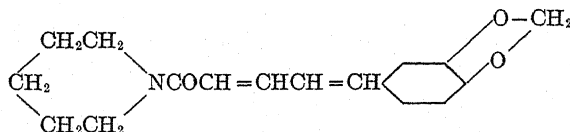
reaction to those of the methyl group of acetophenone.) Devise a synthesis of racemic coniine.

4. How many stereoisomers of ephedrine are possible? What might you obtain in a synthesis from optically inactive material? How would you prepare the optically active drug from such a product? Starting with propionic acid, benzene, and methyl amine, outline the steps in the synthesis of racemic ephedrine.

5. Write equations for the steps in the preparation of 3-aminopyridine from nicotine.

6. Outline the steps in the synthesis of cocaine from simple aliphatic and aromatic compounds.

7. Pterine, the alkaloid from pepper, has the following structure:



What would you predict as to the basic properties of this alkaloid? By what reactions could its structure be established?

8. Devise a possible method of synthesizing procaine.

## CHAPTER XXX

### SYNTHETIC DYES FROM COAL TAR

Through the centuries, countless unrecorded experimenters slowly developed the art of dyeing fabrics. Certain plant and animal products were found to be of value, and their use spread from one ancient people to another. Until the middle of the last century, all dyes were substances which occurred in nature. Their chemical constitutions were unknown, and their synthesis hardly dreamed of. Then came the triumph of the synthetic chemist and the coal tar dye industry.

The first synthetic dyestuff was prepared quite unintentionally by William Henry Perkin in 1856 while still a student in Hofmann's laboratory in London (see footnotes, p. 404 and p. 326). The oxidation of crude aniline was being studied in the ambitious attempt to synthesize quinine. A substance was obtained whose beautiful violet solution was found to dye wool and silk. The young discoverer (Perkin was then but 18) named the substance *mauve*, and against the advice of his teacher set up a factory for its manufacture. Within two years the industrial preparation of the first synthetic dyestuff was an assured success. Many similar discoveries soon followed, and a number of new dyes were manufactured by the oxidation of aniline and other aromatic amines. This first success of the synthetic dyestuff industry was based almost entirely on empirical knowledge. Even the structure of aniline itself was not established at this time! Indeed, it was not till 1865 that Kekulé made possible the next advance of aromatic chemistry by his theory of the structure of benzene.

The history of Perkin's discovery of mauve and the development of its manufacture illustrates one aspect of the development of the coal tar dye industry. The empirical art may run far ahead of the science; even today some of the most important dyes (sulfur colors) are prepared essentially by an empirical procedure, and the structure of the final products is unknown. There are definite

limits to what such empiricism may accomplish in organic chemistry, however. Without the structural theory and its skillful application to the solving of complex problems, the coal tar dye industry would never have reached its present development. The first application of Kekulé's structural theory to the dyestuff industry by Graebe and Liebermann in 1868 marks an advance more important in many ways than the initial discovery of mauve. These investigators started with the natural dye of the madder root, alizarin, and established its structure. Armed with the knowledge thus obtained, they then synthesized alizarin in the laboratory, and within a few years had developed a satisfactory industrial method for its production from coal tar (anthracene). Synthetic alizarin soon drove the natural dye from the market. The story was repeated some thirty years later, when the industrial synthesis of indigo followed the elucidation of its structure by Baeyer, and again the natural dye was supplanted by the cheaper synthetic material.

Today the synthesis of new dyes is based on an enormous amount of exact scientific information. It is possible to outline many complicated syntheses in advance and build up step by step a new substance whose dyeing properties can be foretold in advance. In order to gain a little insight into the basic principles of this most complex science of dyestuff manufacture, we must consider some fundamental facts about colored substances and dyes.

**Color and Chemical Constitution.** The great bulk of the substances hitherto mentioned in this book have been colorless and have yielded colorless solutions. Such solutions appear to our eyes to be perfectly transparent to light, but this is only because the range of light which affects our eyes is so limited (Fig. 33). All organic compounds absorb light of short wave-lengths (ultra-violet light). Such absorption may be studied by means of a photographic plate and a spectroscope which resolves the light transmitted by the liquid. The results (Fig. 33) are called absorption spectra. It is found that unsaturated compounds absorb light of longer wave-length (nearer the visible) than saturated compounds. Certain combinations of unsaturated groups cause the substance to absorb some of the light visible to the eye and the solution is then colored.

Certain unsaturated groupings are definitely associated with

the absorption of visible light, and we can predict that compounds having such groupings will be colored. Such groups which confer

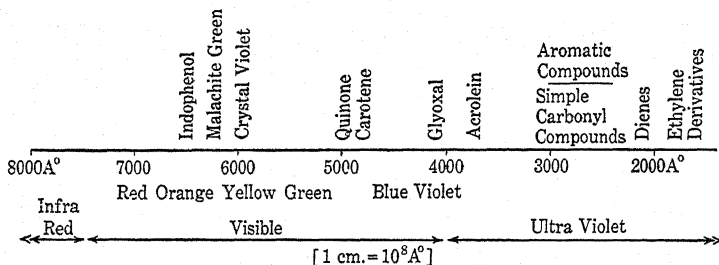
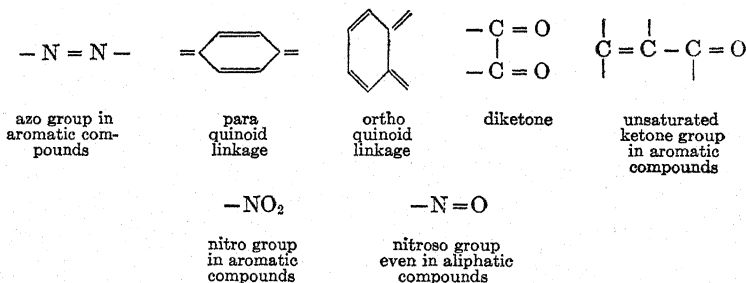


Fig. 33. Diagram showing absorption spectra in the visible and ultra-violet regions.

The approximate position of the absorption band of *longest* wave-length is indicated in each case; many compounds have absorption bands in several positions.

color on a molecule are said to be **chromophoric** groups or **chromophores**. The following are usually regarded as important chromophores:



The presence of one or more aryl groups attached directly to the chromophoric group is usually essential; the introduction of such groups as  $-NH_2$ ,  $-N(CH_3)_2$ ,  $OH$ ,  $OCH_3$ , in the aromatic nucleus intensifies the color.

Clearly any attempt to relate the color of a compound to its structure (chemical constitution) is only one aspect of the broader problem of the relation of structure and absorption spectrum. In a very rough way, we can recognize that certain groupings of atoms usually cause the absorption of a certain range of light, and can even foretell to some extent the absorption spectrum of a compound which contains several such groupings (although the effects are by no means simply additive). By comparing the absorp-

tion spectrum of a substance of unknown constitution with that of a closely related compound of known structure, it is often possible to tell whether or not a certain grouping of atoms is present. If the relation between structure and light absorption were completely understood, it might be possible to determine the constitution of many substances from an examination of their absorption spectra alone. Unfortunately, the absorption of light by the valence electrons of organic molecules is such a complex physical process that it has not been possible so far to subject it to a fundamental analysis. In a general way, it is evident that in saturated compounds the valence electrons absorb only very short wave-lengths of light (extreme ultra-violet), because this light has a high energy content which can affect the tightly bound electrons (the shorter the wave-length of light, the richer it is in energy). Highly unsaturated compounds absorb in addition the longer wave-lengths of visible light, since these contain only sufficient energy to affect the loosely bound electrons of the unsaturated linkages. It can be shown by the use of wave mechanics that according to the electron theory of valence, the absorption of light by a compound should be large and the band far towards the red if *resonance* is possible between two nearly equivalent structures which are connected with a positive or negative charge unsymmetrically placed on the molecule. Beyond such rough qualitative pictures, it is not possible to proceed at present in an attempt to give a fundamental theory of the color of organic compounds.

**The Theory of Dyeing.** A colored substance is not a dye unless it can be applied to a fabric. The fabric must become colored, and the color must be resistant to subsequent washing with soap and water. Many beautiful colored substances have no dyeing properties; that is, they can not be made to adhere to any sort of fabric. These substances are therefore useless from the standpoint of the dyestuff manufacturer. If the colored substance has basic groups ( $-\text{NH}_2$ ,  $-\text{N}(\text{CH}_3)_2$ ) or acid groups ( $-\text{SO}_3\text{H}$ ,  $-\text{COOH}$ ,  $-\text{OH}$ ) in the molecule, a water solution of it will usually dye wool and silk directly. These basic and acid groups which confer dyeing properties in the molecule are called **auxochrome** groups; the parent colored substance is called a **chromogen** and contains, as we have seen, a chromophoric group. This terminology, which was suggested by Otto Witt in 1876, is particularly applicable to the classes of dyes which were then common (acid, basic, and mordant dyes), but is not of much value in regard to certain other types of dyes (vat dyes, ingrain colors). The basic groups which confer dyeing properties on the molecule also usually intensify and deepen the color; the sulfonic acid and carboxyl groups are apt to have the reverse effect. By

many, the term auxochrome is applied only to those basic groups which both deepen the shade and confer dyeing properties on the molecule.

Dyes are usually classified in one of two ways, depending on whether one is interested in their application to fabrics or in the chemistry of their manufacture. From the dyer's standpoint, the dyes are classified according to the way they may be applied; we shall consider this classification first and then turn to the chemist's classification of them according to their structure.

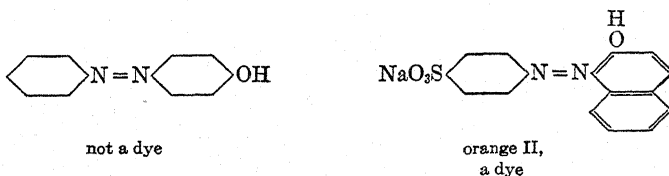
Dyes may be divided into the following classes: (1) acid dyes; (2) basic dyes; (3) direct cotton dyes; (4) ingrain colors; (5) mordant dyes; (6) vat dyes; (7) sulfur dyes. The first four classes of compounds may be illustrated by examples chosen from the *azo dyes*. These contain the chromophoric group  $-N=N-$ , and are all made by the coupling reaction which has already been considered in some detail (p. 380). The relative importance of the various classes may be estimated from the following statistics concerning the manufacture of dyes in the United States in 1936:

CLASS OF DYE	AMOUNT MANUFACTURED IN U. S. A. IN 1936
Acid Dyes	15,974,423 lbs.
Basic Dyes	5,727,303 lbs.
Direct Cotton Dyes	29,907,629 lbs.
Mordant Dyes	6,639,885 lbs.
Vat Dyes	
(a) Indigo	18,039,419 lbs.
(b) Others	16,410,094 lbs.
Sulfur Colors	20,717,889 lbs.
Other Dyes	12,746,989 lbs.

The total is over 119 million pounds, valued at \$63,685,557.

**Acid and Basic Dyes.** The simplest method of dyeing cloth or yarn is to immerse the material for a short time in a boiling solution of the dye, remove, rinse, and dry. Substances which will dye cloth in this way are spoken of as **direct dyes**. It is obvious that a direct dye must be a water-soluble, colored compound, and in addition must have the property of fixing itself on the fabric. Many dyes are direct dyes for animal fabrics (silk and wool), but there are relatively few direct cotton dyes.

The direct dyes have in the molecule either acid groups or basic groups and are classified as acid or basic dyes accordingly. The dyestuff is the salt of the acid or basic compound, and like most other salts, is soluble in water. In addition to making the compound soluble, the acidic or basic group also serves to bind the dye to the cloth in the case of the animal fabrics. There is probably a chemical combination, since the protein material of which animal fabrics are composed can form salts with either acids or bases. Most dyes are not direct to cotton because the carbohydrate has no salt-forming properties.



**Acid Azo Dyes.** The acid group in an acid azo dye is almost always the  $-\text{SO}_3\text{H}$  group. The compound actually used is the sodium salt, but the dye bath is acidified. The phenolic group is

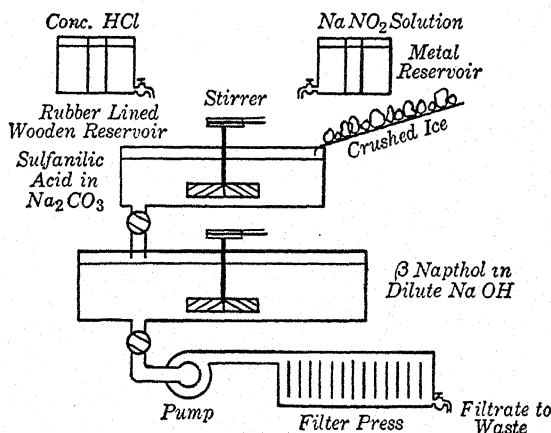
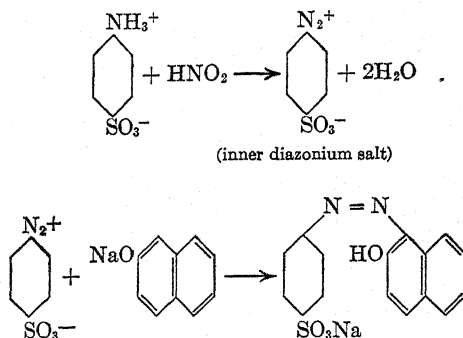


Fig. 34. Cross section of typical azo dye plant. (Preparation of Orange II.)

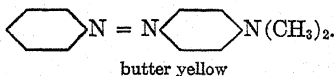
not acid enough to form salts which are essentially neutral. Thus *p*-hydroxyazobenzene is *not* an azo dye; but a similar azo compound, orange II, with the  $\text{SO}_3\text{Na}$  group, is a dye.

The  $\text{SO}_3\text{H}$  group is always introduced into the molecule before the coupling process. Either a sulfonated amine is diazotized and coupled with a phenol, or the sulfonic group is introduced into the phenolic compound before coupling. The dye is the sodium salt of the sulfonic acid and is separated by *salting out*. This process consists in adding common salt until the solution is saturated. Almost all the sodium salts of complex sulfonic acids are insoluble in saturated brine. In the preparation of a common acid dye, **orange II**,  $\beta$ -naphthol (p. 452) is the phenolic substance and sulfanilic acid (p. 367) the primary amine employed:



Industrially, orange II is one of the most important acid dyes.

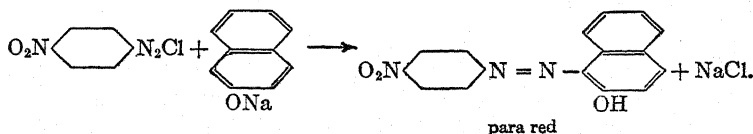
**Basic Azo Dyes.** These dyes are prepared by coupling diazonium salts with amines. They are usually employed as the hydrochlorides, in which form they are soluble in water. The substance commonly employed for coloring butter is **para dimethylaminoazobenzene** (p. 381), known as **butter yellow**. The colors of the azo dyes range all the way from yellow to black according to the number of azo linkages and the nature of the other groups in the molecule.



The scientific nomenclature of dyes is so difficult that trade names are used almost exclusively in speaking of them. These names often give no clue to the chemical structure. Fortunately, there are color indexes published in which the trade names and the structure of most common dyes are given.

The most readily available of these is the Colour Index of the British Society of Dyers and Colourists.

**Ingrain Colors.** A very interesting method of coloring cotton fabric is to form the dyestuff right in the fiber by a chemical reaction. This may be accomplished very readily in the case of the insoluble azo compounds. For example, if cotton cloth is impregnated with an alkaline solution of  $\beta$ -naphthol and then passed through a solution of diazotized para nitroaniline, the bright red azo dye is formed on the fiber.



Dyes which are thus formed on the cloth are called ingrain colors. They are very fast to washing and are much used on cotton.

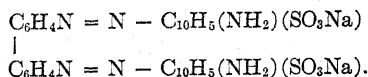
**Developed Dyes.** Developed dyes are a special class of ingrain colors. The cloth is dyed with some dye which contains a primary, aromatic amino group. The cloth is then passed through a cold dilute solution of nitrous acid, and the amino group of the dye is diazotized. The cloth is thus covered with a diazonium salt, and if it passed at once into an alkaline solution of a phenol or amine, a coupling reaction takes place.

**Direct Cotton Dyes.** One group of acid azo dyes for some unknown reason is direct to cotton. They are also direct to wool and silk by virtue of being acid dyes. For this reason, they may be used on mixed materials and are sometimes called **union colors**. The dyes which are sold for household use usually belong to this class since they are designed for use as direct dyes for wool, silk, or cotton.

Practically all the direct cotton dyes have two or more azo linkages and two or more sulfonate groups. They are prepared by the double diazotization and coupling of certain diamines. One of the most important of the diamines which will form direct cotton dyes is **benzidine** (p. 376).

The two primary amino groups in this compound can be diazotized in the usual way, and the di-diazonium salt coupled with sulfonated phenols or amines to give dyestuffs. One of the

simplest of these compounds is **Congo red**, which has the formula,



The compound is prepared from diazotized benzidine and naphthionic acid,  $\text{C}_{10}\text{H}_6(\text{NH}_2)(\text{SO}_3\text{H})$  (1, 4); the coupling takes place in the  $\beta$  position adjacent to the amino group. Congo red suffers from the disadvantage of being sensitive to acids as it turns blue when treated with a mineral acid. (It is sometimes used as an indicator to distinguish strong acids from weak acids, *e.g.*, HCl from  $\text{CH}_3\text{COOH}$ .) The coupling of 3, 3'-dimethylbenzidine (so-called toluidine prepared from ortho nitrotoluene) with naphthionine acid yields a compound having the same structure as Congo red except for two methyl groups adjacent to the azo linkages. It is known as **Benzopurpurin 4B**, and is one of the most important direct cotton colors; it is less sensitive to acids than Congo red.

**Chemical Classification of Dyes.** Dyes may be best classified from a chemical viewpoint by reference to their structure. This determines their method of manufacture, and with certain exceptions all dyes of the same chemical class are prepared in the same general way. The common classes of dyes are: (1) nitrophenolic dyes; (2) azo dyes; (3) triphenylmethane dyes; (4) anthraquinone mordant dyes (*e.g.*, alizarin); (5) indigoids; (6) anthraquinone vat dyes; (7) sulfur dyes. Other small and relatively unimportant classes are known, and some sub-classes of group 3 practically constitute separate groups of substances; one of these includes some dyes prepared from phthalic anhydride which will be considered.

Of the nitro dyes (class 1) picric acid (p. 360) and Martius yellow (2, 4-dinitro alpha naphthol) may serve as examples. The chromophoric group is the nitro group. Because of the strongly acid nature of the phenolic group in the nitrophenols, they are strong acids and are *acid dyes*. They dye wool and silk, but not cotton. This class is not one of the important groups, but does represent the simplest acid dyes.

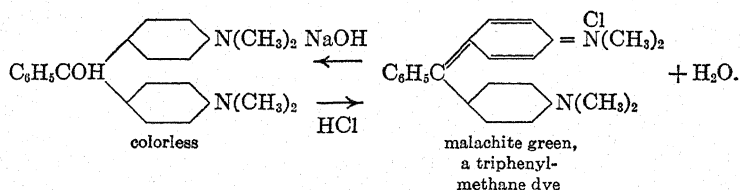
The azo dyes have already been considered in sufficient detail,

since representatives of this group were used to illustrate various types of dyes. All azo dyes are manufactured by a coupling reaction.

### TRIPHENYLMETHANE DYES

The triphenylmethane dyes were the first synthetic dyes, although it was not for twenty years after their first production that their structure was elucidated by Emil Fischer and his cousin Otto Fischer (1876). Perkin prepared mauve by oxidizing crude aniline and shortly afterwards (1859) Hofmann prepared magenta (fuchsine) by oxidizing a mixture of aniline and toluidine. The final products in each case were salts (usually hydrochlorides) of a complex base. The substances are, therefore, basic dyes.

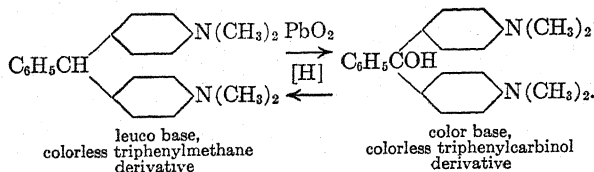
**Structure of Triphenylmethane Dyes.** The chemistry of these complex substances is most readily understood by considering their relation to triphenylcarbinol and triphenylmethane. The derivatives of triphenylcarbinol which have two or more basic groups in the para position form highly colored salts; these are the triphenylmethane dyes. For example, the colorless di-*p*-dimethyl-amino-triphenylcarbinol forms a green hydrochloride which is malachite green.



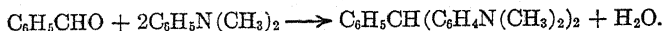
On treating with alkali, the colorless carbinol (known as the **color base**) is formed again. (Compare formation of pseudo bases, p. 518). The structure written for the dye shows a quinoid linkage; this is probably the chromophoric group although the exact formulation of the triphenylmethane dyes is an open question. The chlorine atom is associated with a *pentavalent nitrogen* and is *ionic*.

The triphenylmethane dyes owe their name to the fact that the color bases (carbinols) are readily reduced to derivatives of tri-

phenylmethane. On oxidation of these so-called **leuco bases**, the color base is regenerated:



The leuco base of malachite green is formed by heating benzaldehyde with dimethylaniline and zinc chloride:

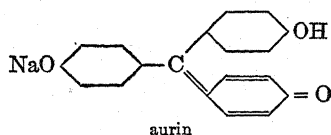


Malachite green is prepared by oxidation of the leuco base and subsequent action of hydrochloric acid.

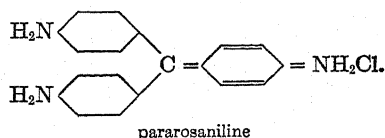
**Resonance of Triphenylmethane Dyes.** An inspection of the formula of malachite green will show that two arrangements of bonds are possible according to whether the quinonoid structure is in the ring written above or below on p. 551. If a substituent were present in one ring but not the other, the two formulas would represent isomers which differed only in the position of the bonds. The reader will recognize that this situation is exactly like that already met with in the case of the guanidinium ion, benzene, and other aromatic compounds. It is not surprising, therefore, that no such isomers have been obtained. Clearly, the two formulas represent two resonating structures, and the triphenylmethane dyes a type of system made more stable by resonating energy. According to the wave-mechanical interpretations of the electron theory of valence, this resonance of an unsymmetrical ion is responsible for the fact that the triphenylmethane dyes are so highly colored. This is the modern statement of a theory which was advanced many years ago and which connected the possibility of an oscillating structure with the high color. It will be seen that if *only one* phenyl group carries a  $\text{NH}_2$  or  $\text{NR}_2$  group, no such oscillation (in modern terms, no resonance) is possible. While compounds containing only one group are colored, they are feebly colored as compared to the dyes. The second basic group is the auxochrome group and both increases the intensity of the color and deepens the shade (moves the band towards the red). The function of the auxochrome group in this case is to introduce the possibility of resonance. Resonance energy also makes the positive ion more stable and favors its formation from the color base (a pseudo base).

The hydroxyl derivatives of triphenylcarbinol illustrate the same principle. If the hydroxyl group is in the para position, such compounds easily lose water to form a quinone-like compound. If one hydroxyl group is present the substance is only feebly colored yellow; if two hydroxyl groups are present *and the sodium salt* is formed by the action of alkali, the color is an

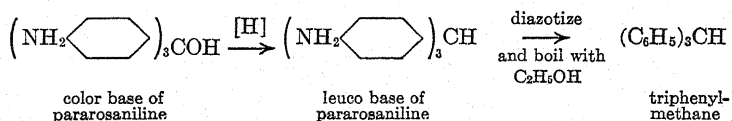
intense reddish violet. The trihydroxy compound is called **aurin**; its sodium salt finds industrial use as a dye.



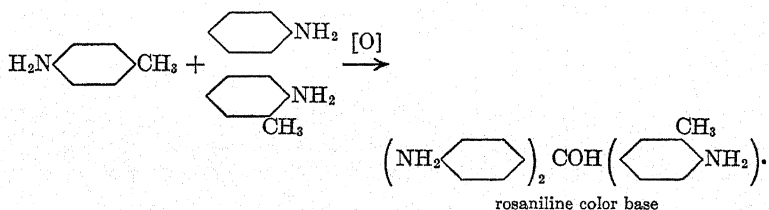
**Fuchsine.** Fuchsine, or magenta, is a triphenylmethane dye prepared by oxidizing a mixture of aniline and the isomeric toluidines. A color base is formed (a triamino-triphenylcarbinol) which on treating with acid forms the dye (a salt). The chief constituent of the dyestuff thus prepared is known as **pararosaniline**. It has the following structure:



On treating with alkali the colorless color base of the compound is formed which on reduction yields triamino-triphenylmethane. This on diazotization and boiling with alcohol (p. 379) forms triphenylmethane; in this manner the constitution of the triphenylmethane dyes was first established:

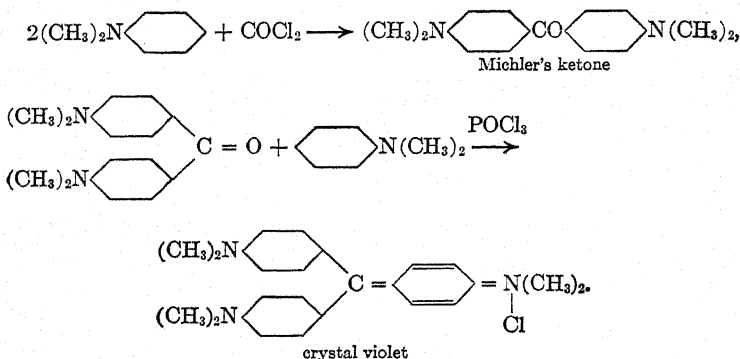


**Other Triphenylmethane Dyes.** A homolog of pararosaniline is known as **rosaniline**. It has a methyl group in the meta position in one ring. It results from the ortho toluidine present in the mixture; pure para toluidine and aniline yield only pararosaniline.



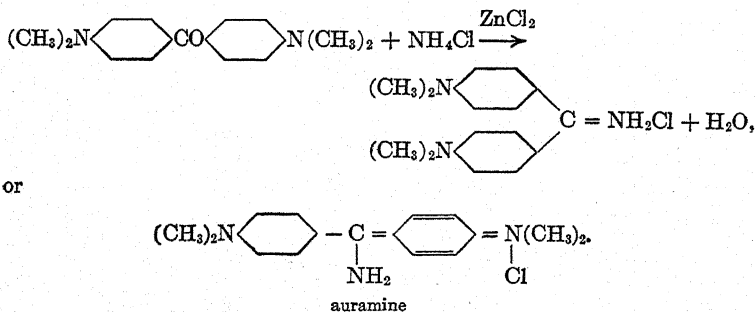
Crystal violet is the hexamethyl derivative of pararosaniline, the methyl groups being substituted for the hydrogen atoms of the amino groups. This substitution changes the color from a red to a bluish violet.

Methyl violet, which contains only five methyl groups, is of a redder shade than crystal violet, as might be expected. These dyes can be made by methylating the parent dye, but are usually synthesized from methylated anilines. The preparation of crystal violet illustrates another method of preparing triphenylmethane dyes. A derivative of benzophenone is condensed with an aromatic amine; the substituted benzophenone is made from phosgene and dimethylaniline:



By sulfonating the triphenylmethane dyes, sulfonic acid groups may be introduced into the molecule, and thus *acid triphenylmethane* dyes are produced.

**Auramine** is a basic dye related to the triphenylmethane dyes, but is really a diphenylmethane dye. It may be prepared by heating Michler's ketone with ammonium chloride and zinc chloride:



The resonating structure of the positive ion of this dyestuff are similar to both those of the triphenylmethane dyes and the guanidinium ion. The intensity of color, the stability of the  $>\text{C}=\text{NH}$  group and the relatively strong basicity are all explained by the resonance of this ion. Auramine is a bright yellow

dye, direct to wool and silk. Almost one million pounds of it were prepared in the United States in 1936 (nearly one sixth of the amount of all the basic dyes manufactured); its most extensive use is in coloring paper.

**Cotton Dyeing with Basic Dyes.** The basic dyes may be applied to cotton by treating the cloth with tannic acid (p. 424), followed by antimony tartrate (tartar emetic). The acid groups of the tannic acid combine with the basic groups of the dyestuff forming an insoluble salt of high molecular weight, which adheres to the cotton. A substance like tannic acid which binds a dye to the fabric is known as a **mordant**. Cotton cloth soaked in a tannic acid solution can be dyed very satisfactorily with the basic dyes. At one time the use of the basic dyes with tannic acid as a mordant was the common method of dyeing cotton. This process has been largely replaced by the direct cotton dyes, the ingrain colors, sulfur dyes, and the vat dyes. Although the basic dyes may be applied to cotton by the use of mordants, they are not classified as mordant dyes. This name is restricted to those dyes which are applied to fabrics by means of a metallic hydroxide as a mordant.

#### ANTHRAQUINONE MORDANT DYES

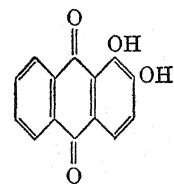
**Mordant Dyes.** Dyes of this class are themselves incapable of dyeing fabrics, but if the cloth is impregnated with a **metallic hydroxide** and boiled with a suspension of the dye a permanent color is formed. The color varies with the nature of the metal. The process is usually carried out by soaking the cloth in a solution of the acetate of the metal. On boiling the fabric, the acetate is hydrolyzed and the metallic hydroxide thus precipitated on the fiber, where it combines with the dye. The salts of aluminum, iron, chromium, and tin are commonly employed. Alizarin is one of the important mordant dyes; with an aluminum mordant, it gives the color known as **Turkey red** which has been much employed on cotton cloth.

If a metallic hydroxide is freshly precipitated in the presence of alizarin or a similar dyestuff, the precipitate is a highly colored compound of the hydroxide and the organic material. Such materials are called **lakes** and are employed as pigments. The color which develops on the fabric during the dyeing process is presumably a lake which is generated directly on the cloth. The

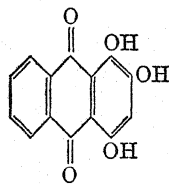
mordant dyes all contain one or more phenolic hydroxyl groups which are undoubtedly involved in the combination with the metallic hydroxides. The lakes are to be regarded as complex metal salts of the dyes; only the salts of certain phenols, however, have sufficient stability towards hydrolysis to be true lakes. Perhaps the most important grouping which results in the formation of real lakes is that which occurs with alizarin, whose structure we shall now consider.

**Alizarin.** Alizarin was once one of the most important dye-stuffs. It occurs in madder root and enormous quantities of madder were formerly cultivated in Asia and in Europe for the production of the dye. After the synthetic production of the substance from coal tar, the cultivation of madder was given up. Alizarin gradually lost its predominant position by the advent of the synthetic dyes for cotton. The use of mordant dyes, including alizarin, has greatly declined in the last fifty years, and in 1936 only 58,138 lbs. of alizarin were manufactured in the United States.

Alizarin is 1, 2-dihydroxyanthraquinone, and it occurs in the madder root as a glucoside. This glucoside is readily hydrolyzed by enzymatic action or by dilute acids liberating the dyestuffs. Together with alizarin in the madder root are various other



alizarin  
1, 2-dihydroxyanthra-  
quinone



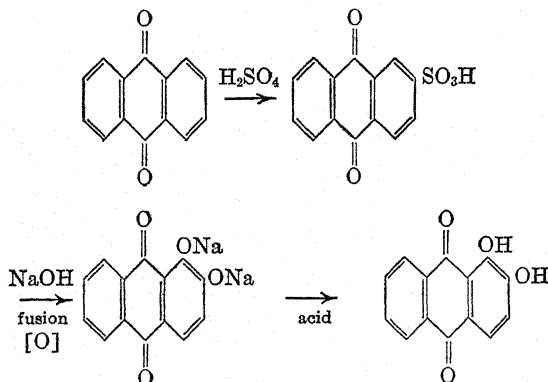
purpurin  
1, 2, 4-trihydroxyanthra-  
quinone

hydroxyanthraquinones as glucosides. The most important of these is purpurin; it is also a mordant dye, and its presence in the madder extracts affected the shade of the dye somewhat.

The fact that alizarin was an anthracene derivative was established by heating it with zinc dust. Under these drastic conditions the compound was reduced to anthracene. This discovery of Graebe and Liebermann's was soon followed by its synthesis from anthraquinone, which was accomplished by introducing two bromine atoms and fusing the dibromo compound with

alkali. This synthesis proved that alizarin was a dihydroxyanthraquinone. The exact location of the two hydroxyl groups was not established, however, until some years later. The chromophoric group in alizarin is the quinone portion of the molecule.

Alizarin is now prepared from anthraquinone. The latter is sulfonated and the sodium salt of the sulfonic acid fused with sodium hydroxide. Not only is one hydroxyl group thus intro-



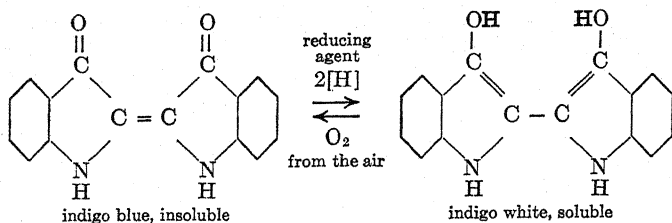
duced into the molecule, as would be expected, but a second is also formed by the oxidizing action of the atmosphere (see phloroglucinol, p. 391):

#### VAT DYES

Indigo is the oldest example of the vat dyes. They are applied to cotton and to animal fabrics by a peculiar process which is akin to ingrain dyeing (p. 549). All vat dyes are highly colored, insoluble powders which pass into water-soluble compounds when treated with alkaline reducing agents. The reduction is carried out in a *vat* (hence the name vat dye), and the cloth or yarn is passed through the solution of the reduced dye. On exposure to the air for a short time, the reduced form of the dye is reoxidized by the atmospheric oxygen with the formation of the original insoluble substance. This material is thus regenerated right in the fiber of the cloth and, therefore, like the ingrain colors, the vat dyes are very fast.

There is always a color change in vat dyeing; in the case of indigo, the soluble reduced form is colorless and is known as *leuco*

indigo or indigo white. Vat dyeing with indigo may be represented by the following equation; the two hydrogen atoms which are gained in the reduction and lost in the oxidation are printed in heavy type.

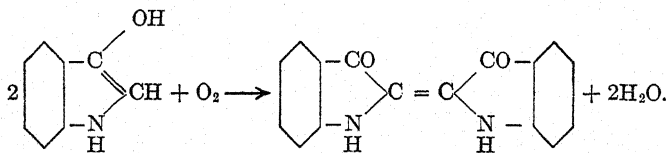


Sodium hydrosulfite,  $\text{Na}_2\text{S}_2\text{O}_4$ , is the reducing agent which is now commonly employed with vat dyes; glucose and alkali may also be employed and in former times a fermentation was used to reduce the dye.

**Natural Indigo.** A number of plants, especially species of *indigofera* which flourish in semi-tropical countries, contain a glucoside known as *indican*. This glucoside on hydrolysis yields a

molecule of glucose and one of **indoxyl**,  $\text{C}_8\text{H}_7$   $\text{CH}$ . The

latter substance is rapidly oxidized by air forming indigo:



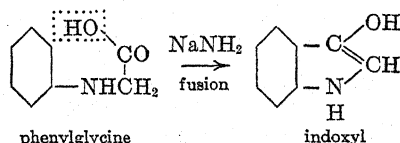
The branches and leaves of the plant are immersed in water and a fermentation takes place in the course of a day liberating the indoxyl. The solution is then stirred vigorously with paddles and the indigo which is formed by the action of the air rises as a dark blue scum.

**Synthetic Indigo.** After the constitution of indigo and indoxyl was established by Baeyer<sup>1</sup> in 1882, the industrial chemists turned


<sup>1</sup> Adolph von Baeyer (1845-1917), Professor at the University of Munich for forty-two years. The Munich laboratory has played an important part in the development of organic chemistry. Baeyer was the successor to Liebig, one of the founders of experimental organic chemistry, and was followed by Richard Willstaetter, who determined the structure of the coloring materials of flowers.

their attention to the problem of its synthesis from coal tar. The problem obviously resolves itself into the synthesis of the relatively simple substance indoxyl, since this can be readily converted into indigo by atmospheric oxidation.

A number of different syntheses of indigo were devised and several have been operated on a large scale. The first successful process started with **phthalic anhydride** which was cheaply obtained by the oxidation of naphthalene (p. 448). This method has now been replaced by the so-called **phenylglycine method** which starts with aniline. This is heated with monochloroacetic acid which is easily prepared by the chlorination of acetic acid



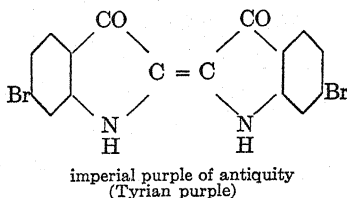
(p. 100). The action of aniline on chloroacetic acid yields **phenylglycine**,  $\text{C}_6\text{H}_5\text{NHCH}_2\text{COOH}$ . This substance on fusion with sodium hydroxide and sodamide,  $\text{NaNH}_2$ , produces indoxyl.

The first product of the reaction is probably  $\text{C}_6\text{H}_4$    $\text{CH}_2$  which

passes into indoxyl by the shift of an hydrogen atom (enolization). No attempt is made to isolate the indoxyl. The reaction mixture is dissolved in water and agitated with air; the indigo soon separates as an insoluble powder. The synthetic indigo has now practically driven the natural product from the market. It is perhaps the most important single dyestuff now in use; in 1936 over 18,000,000 pounds were prepared in the United States alone.

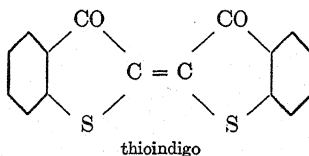
**Indigo Dyes of Antiquity.** Indigo was used as early as 1500 B.C.; mummies of the Eighteenth Dynasty have been found in Egypt with wrappings colored with this dye. The famous imperial purple of the Romans was a dibromo derivative of indigo which was obtained from certain shellfish along the Mediterranean coast. The identity of this dye has been established with certainty by a recent examination of these shellfish. In this investigation,

12,000 specimens yielded only 1.4 grams of the pure substance whose structure was established by its analysis, reactions, and comparison with a sample of synthetic material.



The dibromoindigo so highly prized 2000 years ago is not manufactured today because similar shades can be produced by other dyes which are cheaper to prepare. Tribromo and tetrabromo derivatives of indigo are, however, important vat dyes. They are manufactured by the direct bromination of indigo.

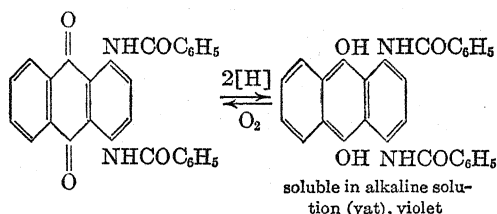
**Indigoids.** Indigo, its halogenated derivatives, and certain related compounds of analogous structure are sometimes referred to as the indigoids. They represent one subdivision of the larger class of vat dyes. Thioindigo is a red vat dye which has a structure analogous to indigo except that a NH group is replaced by a sulfur atom. It forms a vat color in exactly the same way as indigo, and is applied in the same manner.



Thioindigo and some of its derivatives are important dyes, and are prepared in considerable quantities. The chromophoric group in the indigoids is the linkage  $O = \overset{|}{C} - \overset{|}{C} = \overset{|}{C} - \overset{|}{C} = O$ .

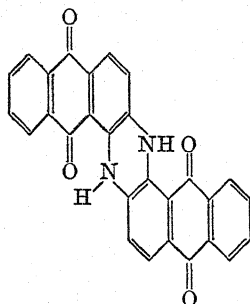
**Anthraquinone Vat Dyes.** Perhaps the simplest representative of this important class is **algal red**. This is the dibenzoyl derivative of 1, 4-diaminoanthraquinone; it is a scarlet red vat dye which is applied exactly like the indigoids. The reduced, soluble form of the dye is the anthrahydroquinone. As we have seen, anthrahydroquinone is easily oxidized by air, and this fact is one of the underlying principles involved in the use of anthra-

quinone derivatives as vat dyes:



The "vats" prepared from the anthraquinone vat dyes are usually highly colored.

The first anthraquinone vat dye was prepared in 1901 by fusing beta aminoanthraquinone with alkali. Two molecules condensed together. The product is known as **indanthrene blue**.



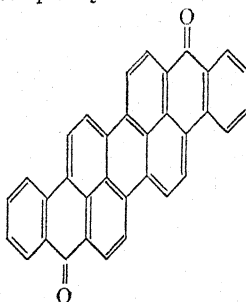
indanthrene blue

The anthraquinone structure is intact in this dye, and it is reduced in the vat to an anthrahydroquinone derivative which is soluble in alkali.

The anthraquinone vat dyes are highly valued for use on cotton. They are extremely fast to washing and to light. They are expensive to manufacture and are sold at a high price. The relatively small production of this class of dyes (see p. 546) is not a true measure, therefore, of their economic importance.

A number of important vat dyes have been synthesized which contain eight or nine benzene rings condensed together with but two carbonyl groups. They may be regarded as the quinones of polynuclear aromatic hydrocarbons. On reduction, they pass into alkali-soluble hydroquinones which are easily

oxidized by the air. The formula of one of these substances is of interest because of its very great complexity.



indanthrene violet (nine rings)

These substances are of very high molecular weight and very high carbon and low hydrogen content. (Indanthrene, C = 89.6; O = 6.8; H = 3.6 per cent.) Therefore, as would be expected, they are insoluble in practically all solvents, are non-volatile, and have extremely high melting points. They are tremendously resistant to attack by even vigorous reagents. For this reason, they are the fastest of all known dyes, and can only be removed from a fabric by the action of an alkaline reducing agent which converts them into the hydroquinone (vat) form.

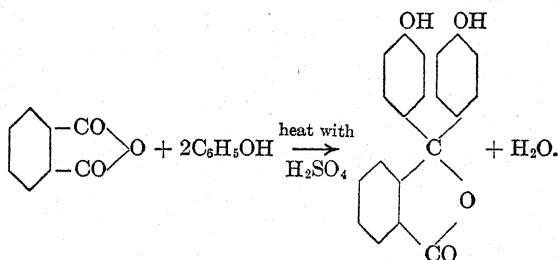
#### SULFUR DYES

The sulfur dyes are a group of compounds of unknown structure prepared by heating certain aromatic amines, nitrophenols, or aminophenols with either sodium polysulfide or sulfur. A condensation of several molecules occurs; nitro groups (if present) are reduced and sulfur enters the molecule. The sulfur dyes are usually applied by dissolving them in sodium sulfide solution and dyeing the cloth in such hot solutions. A sort of vat dyeing is probably involved in this operation; sodium sulfide is a reducing agent and renders the sulfur dyes soluble by reducing them to a more acidic form. On exposure to air, reoxidation occurs, and the insoluble dye is left in the fiber. The sulfur colors are used for cotton; they include a number of very good blue, green, yellow, and black dyes.

**Sulfur Black.** This dye is prepared by heating 2, 4-dinitrophenol or 2, 4, 6-trinitrophenol with a concentrated solution of sodium polysulfide. The preparation of the nitrophenol was outlined on p. 361. The output of sulfur black was over 14,000,000 lbs. in 1936 in the United States, a larger quantity than for any other single dyestuff except indigo.

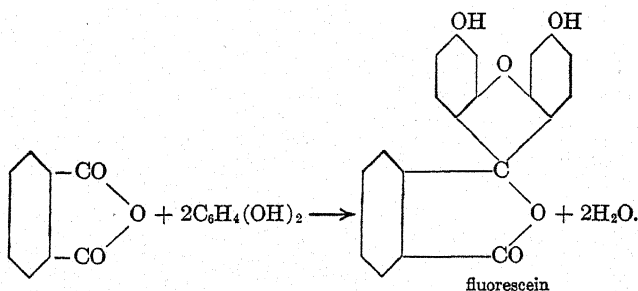
## DYES FROM PHTHALIC ANHYDRIDE

**Condensation Reactions of Phthalic Anhydride.** The carbonyl group in phthalic anhydride is reactive and enables the compound to enter into a variety of condensation reactions, some of which lead to interesting and useful substances. When phthalic anhydride is heated with a catalyst (a so-called condensing agent) and an aromatic compound having a reactive ortho or para hydrogen atom, water is eliminated and a complex compound results. The reaction with phenol is the simplest case. It takes place when the two substances are melted together with anhydrous zinc chloride or sulfuric acid:



The product, **phenolphthalein**, is a colorless solid only slightly soluble in water. It is manufactured in considerable quantities for use as a laxative. Its use as an indicator will be discussed shortly.

**Fluorescein and Eosin.** When phthalic anhydride is heated with resorcinol and a condensing agent (zinc chloride), a compound known as **fluorescein** is produced:



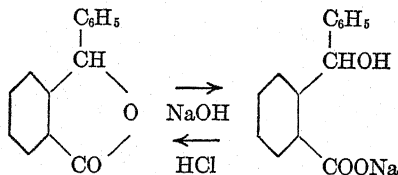
This substance is an orange powder which is only very slightly soluble in water but dissolves in alkaline solution (as a salt). A dilute solution has a brilliant *green-red fluorescence*. The tetrabromo derivative of fluorescein is known as **eosin**. It is a red

powder, soluble in alcohol, and insoluble in water ("spirit-soluble eosin"). Its disodium or ammonium salt is "water-soluble eosin." It is used as a direct dye for silk and as a biological staining material. Red ink is usually a dilute solution of water-soluble eosin.

**Mercurochrome** is a mercury derivative of dibromofluorescein. The group  $\text{HgOH}$  has replaced one of the hydrogen atoms attached to an aromatic ring. The introduction of a mercury atom is often spoken of as mercuriation; it conveys strong antiseptic properties to the molecule. Mercurochrome is a bright red, water-soluble solid which is used in dilute solution as an antiseptic.

#### PHENOLPHTHALEIN AS AN INDICATOR

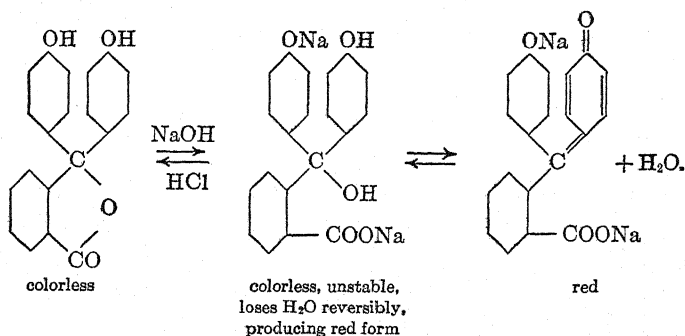
In the titration of acids and bases, phenolphthalein is often used as an indicator. It is red in alkaline solution and colorless in acid solution. This change of color is due to a change of structure. To understand this somewhat complicated reaction, we shall have to recall the behavior of the class of substances known as lactones (p. 213), of which phenolphthalein is a complex example. As we have seen, certain hydroxy acids form lactones very rapidly and the reaction goes to completion. In such a case the free hydroxy acid is unknown; only the sodium salt can be isolated. An illustration of this is shown below.



The lactone is formed *at once* on the acidification of a solution of the salt in the example given above. On treating with alkali, the ring is opened and the salt is formed.

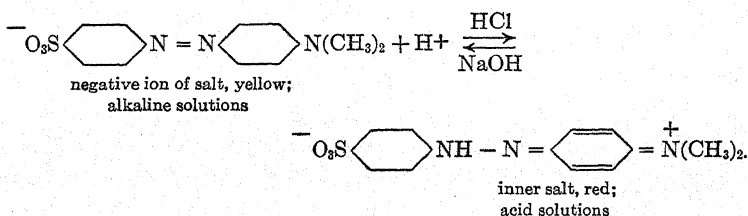
**Color Change of Phenolphthalein.** Returning now to phenolphthalein, it is evident that the lactone ring in this substance resembles closely that in the compound just mentioned. In phenolphthalein, also, the lactone ring is very rapidly opened and closed by making the solution alkaline or acid. In addition to this opening and closing of the ring, however, another change occurs which causes a red color to appear in alkaline solution. The hydroxy

compound loses water, forming a quinone-like structure in one ring; in addition, one of the other phenolic groups forms a salt. All these changes are practically instantaneous. The chromophoric group in the colored (alkaline) form of phenolphthalein is the quinoid structure.




The highly colored ion of phenolphthalein has the same type of structure as aurin (p. 554). The deep color is attributable to the resonance of a negative ion; the hydroxyl group of the phenol as well as the carboxyl group is ionized in the colored form.

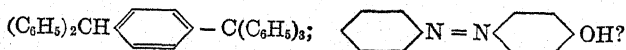
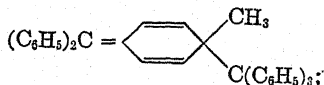
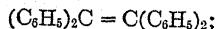
**Other Indicators.** There are a great many organic compounds which are used as indicators. Some of them are similar to phenolphthalein in structure, and the reason for the change in color is essentially the same. With the others, an entirely different set of chemical reactions is involved. In every case, however, there is a practically instantaneous change (or changes) of structure in acid or alkaline solution which alters the chromophoric group in the molecule. As an example of another type of indicator, **methyl orange**, or **helianthin**, may be cited. This is a common indicator which turns in a somewhat more acid solution than phenolphthalein. The change is probably to be represented by the following formulas:



Methyl orange is readily prepared by diazotizing sulfanilic acid and coupling it with dimethylaniline. It can be isolated either as a solid sodium salt (orange) or in the "inner salt" form, a violet colored solid. **Methyl red** is prepared by coupling diazotized anthranilic acid (p. 420) with dimethylaniline. It is yellow in alkaline solution, and red in acid solution; the reasons for the color change are probably exactly like those of methyl orange.

### QUESTIONS AND PROBLEMS

1. Write the structural formulas for eosin, fluorescein, orange II, alizarin, indigo white, butter yellow.
2. Explain the color changes which take place when a solution of phenolphthalein is treated with alkali and then acid.
3. Write equations showing the use of diazonium compounds in the manufacture of azo dyes and ingrain colors.
4. Outline the steps in the preparation of malachite green from coal tar.
5. Compare the action of reducing agents on triphenylmethane dyes, azo dyes, indigo, and vat dyes.
6. Classify dyestuffs according to methods of applying them to the fiber. Give an example of each class.
7. Outline the steps in the synthesis of indigo and alizarin. Show how the latter substance may be prepared without employing anthracene.
8. Write equations showing the chemical reactions involved in the application of vat dyes.
9. Which would you expect to be the stronger base,  $(\text{C}_6\text{H}_5)_2\text{C} =$    $= \text{NH}$  or pararosaniline? Give the reason for your answers.
10. Which of the following substances would you predict to be colored:



Why could not any of the above colored substances be utilized as dyes?

11. Define the following terms: mordant, chromophore, acid dyes, indigoid, indicator, leuco form, color base, Michler's ketone.

12. Discuss briefly the relation of chemical constitution to color, pointing out what other groups are necessary to make a substance a good dye.
13. Starting with products found in coal tar, outline the steps for the preparation of Congo red or benzopurpurin 4B.
14. Outline the proof of the structure of a triphenylmethane dye.

## CHAPTER XXXI

### THE AMINO ACIDS AND PROTEINS

**Occurrence of Proteins.** Fats, carbohydrates, and proteins are the three great classes of compounds which are of prime importance to the biologist and biochemist. We have already considered the first two of these classes and shall devote this chapter to the proteins alone. Proteins occur widely distributed in both plants and animals and are an essential constituent of foodstuffs. When vegetable products are consumed by an animal, the vegetable proteins are decomposed in the processes of digestion, and from the fragments thus formed the animal resynthesizes his own proteins. These animal proteins are in part in solution (*e.g.*, in the blood) but the larger portion consists of the insoluble materials of which the animal tissues are composed. Thus, skin, hair, muscle tissue, and the horny material of nails, horns, and hoofs are essentially proteins. Thus, the proteins serve as structural materials for animals much as the polysaccharides (*e.g.*, cellulose) do for plants. Proteins, like fats and carbohydrates, may also be used as a source of energy when they are consumed by animals. In plants, proteins are found in all the living parts but usually in relatively small quantities except in the seeds.

**Relation of Proteins to Amino Acids.** In their physical properties proteins differ widely from one another. The water-soluble material, white of egg, the partially soluble gelatine, and the insoluble hide of animals are all proteins. In one fundamental respect all proteins are similar — by boiling with dilute acid they are all hydrolyzed to a mixture of **alpha amino acids**. Twenty-four different amino acids have been isolated from the hydrolysis of a variety of proteins. These substances are the building blocks out of which the complex protein molecules are constructed. Therefore, before proceeding further we must consider briefly the amino acids themselves.

## AMINO ACIDS

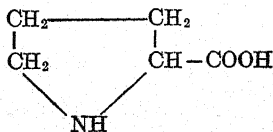
The amino acids are classified according to the relative positions of the amino group and carboxyl group. The nomenclature follows the same principle as is used with the halogen and hydroxyl derivatives of acids (p. 211). Thus **alpha amino-butyric acid** is  $\text{CH}_3\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$  and **beta amino-butyric acid** is  $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{COOH}$ . Fortunately, the amino acids which are formed by the hydrolysis of proteins are all of one class. They are alpha amino acids and we shall confine our attention to them.

**Alpha Amino Acids from Proteins.** The amino acids which have been isolated from the mixtures obtained by hydrolysis of a great variety of proteins are listed below for reference. The student is advised to familiarize himself with the special names and formulas of one or two representatives of each of the three groups into which the acids are divided. The special names are used in this field to the almost complete exclusion of a rational nomenclature.

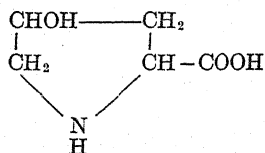
## AMINO ACIDS OBTAINED BY THE HYDROLYSIS OF PROTEINS

**A. Acids with equal number of basic and acid groups** (one each except No. 17).

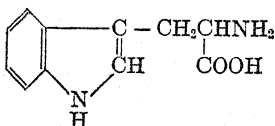
1. Glycine (Glycocol):  $\text{CH}_2(\text{NH}_2)\text{COOH}$
2. Alanine:  $\text{CH}_3\text{CH}(\text{NH}_2)\text{COOH}$
3. Valine:  $(\text{CH}_3)_2\text{CHCH}(\text{NH}_2)\text{COOH}$
4. Leucine:  $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_2)\text{COOH}$
5. Norleucine:  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
6. Isoleucine:  $\text{C}_2\text{H}_5\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{COOH}$
7. Phenylalanine:  $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
8. Tyrosine:  $p\text{-HOC}_6\text{H}_4\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
9. Threonine:  $\text{CH}_3\text{CHOHCH}(\text{NH}_2)\text{COOH}$
10. Serine:  $\text{CH}_2\text{OHCH}(\text{NH}_2)\text{COOH}$
11. Proline:



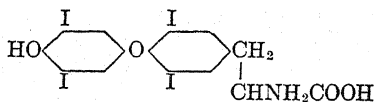
12. Hydroxyproline:



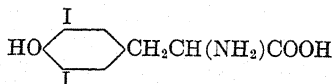
13. Tryptophane:



14. Thyroxine:



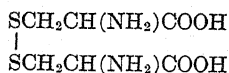
15. Iodogorgoic Acid:



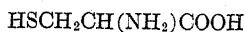
16. Methionine:



17. Cystine:



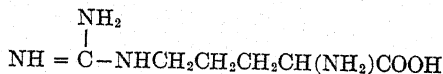
18. Cysteine:

**B. Basic Amino Acids** (several basic groups and one acid group).

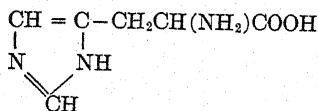
1. Lysine:



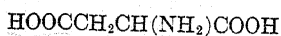
2. Arginine:



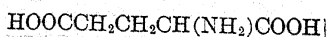
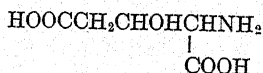
3. Histidine:

**C. Acid Amino Acids** (several acid groups and one basic group).

1. Aspartic Acid:



2. Glutamic Acid:

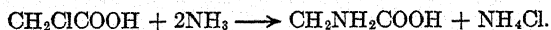
3.  $\beta$ -Hydroxyglutamic Acid:

The alpha amino acids have been classified above according to the relative number of acid and basic groups in the molecule. The importance of this relationship from the point of view of the behavior of the substances will soon become apparent. Although tryptophane has a cyclic  $\text{>NH}$  group in addition to the  $\alpha$ -amino group, it is placed in group A because the second nitrogen atom has no basic properties. On the other hand, the  $\text{>NH}$  groups in the saturated rings in proline (A 11) and hydroxyproline (A 12) and in the heterocyclic ring in histidine (B 3) are basic. The phenolic group in tyrosine is weakly acidic; if this group is counted as an acid group, tyrosine would be put in class C.

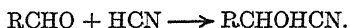
With the exception of glycine ( $\alpha$ -amino acetic acid) all the  $\alpha$ -amino acids contain one or more asymmetric carbon atoms. Therefore, as would be expected, those amino acids which are prepared from proteins are optically active.

In the isolation of amino acids from protein hydrolysates, advantage is taken of the separation into groups according to the solubility of the acids and their salts. The acids in group A are, with the exception of tyrosine (8) and the closely related iodine compounds (14 and 15), all very soluble in water but insoluble in anhydrous alcohol. They may be extracted from their aqueous solutions with *n*-butyl alcohol by continuous extraction (the butyl alcohol layer is saturated with water). When the butyl alcohol solution is rendered water-free by distilling off a portion of the alcohol which carries the water with it, all the acids, except proline and hydroxyproline, crystallize from the solution. The separation of this mixture into its constituents is a matter of great difficulty. Of the amino acids which are not extracted by butyl alcohol, those of group B form insoluble salts with phosphotungstic acid and can thus be precipitated by this reagent. The further separation of the acids of this class and those of class C usually depends on the differential solubility of certain salts in different solvents.

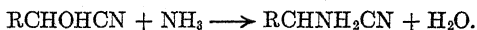
**Synthesis of Alpha Amino Acids.** There are several important methods of synthesizing  $\alpha$ -amino acids in the laboratory. The corresponding simple acid may be halogenated in the alpha position by the action of chlorine or bromine on the acid or the acid chloride. We have already met this reaction in the preparation of chloroacetic and  $\alpha$ -chloro-propionic acids (p. 100). On treatment with ammonia,  $\alpha$ -chloro or bromo acids readily yield  $\alpha$ -amino acids:



A closely related procedure involves the Gabriel synthesis (p. 427) starting with an alpha bromo ester. Another method of synthesis starts with an aldehyde. This is treated in an aqueous or alcoholic solution with sodium cyanide and ammonium chloride. Solutions of a cyanide always contain considerable free hydrocyanic acid from hydrolysis (hydrocyanic is a very weak acid), and this hydrocyanic acid adds to the aldehyde forming a cyanohydrin (p. 117):

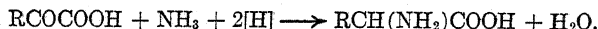


The alkali formed by the hydrolysis ( $\text{NaCN} + \text{H}_2\text{O} \rightleftharpoons \text{NaOH} + \text{HCN}$ ) liberates ammonia from the ammonium chloride, and this reacts with the cyanohydrin:



The amino cyanide,  $\text{RCHNH}_2\text{CN}$ , is thus directly formed by the interaction of the aldehyde and the two inorganic substances. The  $\alpha$ -amino cyanide may be hydrolyzed to an  $\alpha$ -amino acid by boiling with dilute acid.

Finally, the preparation of alpha amino acids by the reduction of alpha keto acids in the presence of ammonia should be mentioned:

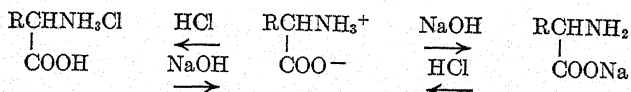


**Amino Acids as Inner Salts.** In discussing sulfanilic acid it was pointed out that its physical properties and chemical behavior are best represented by the "inner salt formula." The amino acids are also inner salts; they may be written as,  $\text{RCHNH}_3^+$ . As in



the case of sulfanilic acid, most of the solid amino acids have a surprisingly high melting point (above  $230^\circ$ ) and are only slightly soluble in organic solvents (though they are readily soluble in water).

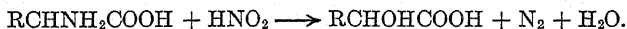
The amino acids themselves are amphoteric substances (p. 393); when treated with either mineral acids or strong bases, they form crystalline salts which are soluble in water.



This amphoteric property of amino acids we shall see later is reflected in the behavior of certain proteins. The amino acids of class A (p. 569) are themselves essentially neutral and form salts with one molecule of either an acid or a base. Solutions of those containing several basic groups (class B), on the other hand, are alkaline and those of class C weakly acid. The former will react with two molecules of a mineral acid and only one of base, while with the latter the situation is just reversed. In both instances *one amino group and one carboxyl group may be regarded as internally neutralized*; the remaining basic or acid group is free to exert its normal function.

The total net electrical charge on the organic molecule will clearly depend on the acidity of the solution. In acid solution the amino acid will be present as a positive ion,  $\text{RCHNH}_3^+\text{COOH}$ , in alkaline solution as a negative ion,  $\text{RCHNH}_2\text{COO}^-$ , and at a certain acidity the *net* charge will be zero since the molecule has the structure  $\text{RCHNH}_3^+\text{COO}^-$ . In acid solutions, the amino acids migrate to the cathode (-) when the solutions are electrolyzed; in alkaline solutions, the molecules move to the anode (+). At a definite hydrogen ion concentration, when the net charge is zero, the compound moves neither to the cathode nor to the anode. This point is known as the **isoelectric point**. Its value depends on the relative strengths and number of acid and basic groups in the amino acid molecule.

**Reactions of Amino Acids.** As would be expected, the  $\alpha$ -amino acids show the characteristic reaction of both organic acids and primary aliphatic amines. They are readily esterified in the usual manner and the esters may be purified by distillation. This fact may be taken advantage of in the separation of the acids of group A. The reaction with nitrous acid liberates nitrogen and forms an hydroxy acid (p. 160). This is the basis of a convenient quantitative method used in studying amino acids and proteins.

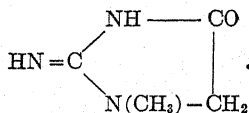


**Creatine.**  $\text{NH}_2\text{C}(=\text{NH})\text{N}(\text{CH}_3)\text{CH}_2\text{COOH}$ . In addition to the amino acids which have been obtained from the hydrolysis of proteins (listed above), a few others also occur in nature. The most important of these is creatine, which may

be regarded as derived from glycine since it contains the chain  $\text{N}-\text{CH}_2\text{COOH}$ .

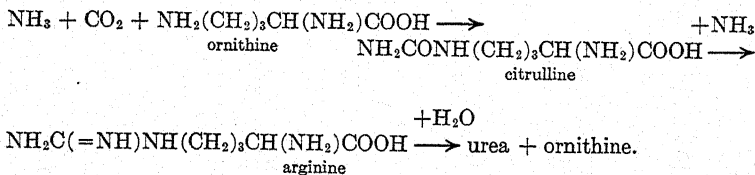
Creatine is present in muscle tissue partially free and partially combined (amide linkage) with the phosphoric acid group. Creatine phosphoric acid together with adenylic acid pyrophosphate (p. 527) are involved in the changes which take place during contraction and relaxation of muscle.

Small amounts of creatine are normally excreted in the urine in the form of the cyclic compound **creatinine**.



Creatinine also occurs widely distributed in plants; it is easily formed from creatine by warming an aqueous solution containing a little mineral acid. When treated with alkali, creatinine forms the salt of creatine. We are here dealing with the opening and closing of a ring very similar to that which occurs in lactones (p. 213).

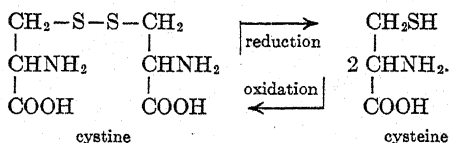
**Ornithine.** Another alpha amino acid, not itself a product of protein hydrolysis but closely related to one of the twenty-four acids, is  $\alpha$ ,  $\delta$ -diamino valeric acid,  $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$ , known as **ornithine**. It is produced in the liver by the hydrolysis of arginine by the enzyme **arginase**. It has been shown that ornithine goes through a cyclic process by which the liver synthesizes urea from ammonia and carbon dioxide. Each step is brought about by an enzyme but in only the last can the transformation be brought about outside the intact cell by an enzyme preparation (**arginase**, see p. 593).



Although we have no information as to the way the plant or animal cells synthesize the various amino acids, it is interesting to

note the close relationship of arginine to histidine (ring closure with loss of hydrogen and ammonia) and of ornithine to proline (ring closure with loss of ammonia). Hydroxyproline is obviously closely connected. Tryptophane may be considered as N-phenyl-ornithine in which ring closure and dehydrogenation have taken place. Thus, the ornithine skeleton  $\text{N}-\text{C}-\text{C}-\text{C}-\text{CH}(\text{NH}_2)-\text{COOH}$  occurs in arginine, histidine, tryptophane, proline, and hydroxyproline. Glutamic and hydroxy glutamic acids contain the same carbon skeleton but no second nitrogen atom.

**Cysteine and Cystine.** Cystine is a disulfide (p. 267) which on reduction readily forms two molecules of cysteine, which contains the mercaptan group. On oxidation cysteine forms cystine:

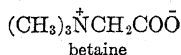


The oxidation of cysteine to cystine is brought about even by the air. In many proteins it is probably cysteine and not cystine which is really present. Cysteine and cystine, like quinone-hydroquinone, form a strictly reversible oxidation-reduction system. Unlike the quinones, however, the speed at which equilibrium is attained in aqueous solutions in the case of the sulfur compounds may be slow. Proteins or polypeptides containing cystine may be involved as catalysts in oxidation-reduction processes in nature; in the presence of suitable enzymes, the oxidation of the SH group to S-S and the reduction of the latter becomes as rapid as the corresponding changes in the hydroquinone system.

**Other Related Substances.** The decarboxylation of the amino acids results in the formation of a variety of nitrogenous bases. The process occurs in nature during putrefaction and decay. Thus arginine (by way of ornithine) yields putrescine,  $\text{NH}_2(\text{CH}_2)_4\text{NH}_2$  (p. 169). Skatole,  $\beta$ -methylindole, a substance with a very disagreeable odor, is formed from tryptophane. By a bacterial decomposition, tryptophane is also degraded to  $\beta$ -indole acetic acid which is present in urine.  $\beta$ -Indole acetic acid is important in plant biochemistry as it is a growth-regulating substance for plants. For this reason it is classified as one of the plant hormones and is known as **heteroauxin**.

Glycine is frequently found in the form of its acyl derivatives. The glycocholic acid of bile (p. 495) is one example. Benzoyl glycine or **hippuric acid**,  $\text{C}_6\text{H}_5\text{CONHCH}_2\text{COOH}$ , found in the urine of horses, is another.

**Betaine** is a derivative of glycine in which the nitrogen atom has been converted into a quaternary ammonium salt by complete methylation. Since the resulting base is very strong (see p. 167) the compound exists entirely as an "inner salt."



Since betaine is an inner salt of a strong base and a weak acid (a substituted acetic acid), it will form a hydrochloride,  $[(\text{CH}_3)_3\overset{+}{\text{N}}\text{CH}_2\text{COOH}]\text{Cl}^-$ , but not a sodium salt. In the hydrochloride the ionization of the weak acid has been suppressed by the mineral acid. Betaine occurs widely distributed in plants and has also been found in animal tissue. It can be obtained from the residues of beet sugar molasses or prepared synthetically by methylating glycine. It is a crystalline solid with a very high melting point (like glycine itself); it is very soluble in water from which it crystallizes with a molecule of water of crystallization. It is interesting to note that choline (p. 190) is the primary alcohol corresponding to betaine.

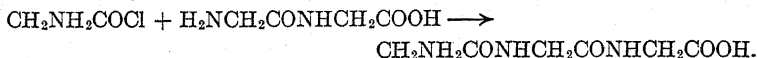
### PEPTONES AND POLYPEPTIDES

Proteins are completely hydrolyzed to amino acids by boiling for several hours with 10 per cent sulfuric acid or 30 per cent hydrochloric acid. The decomposition is also brought about by **enzymes**. These are involved in the digestion of proteins. **Pepsin** is present in the stomach and acts in a somewhat acid solution; **trypsin**, which occurs in the pancreatic juice, and **erepsin**, in the intestines, are involved also in the complete disintegration of the complex molecule. Each animal undoubtedly resynthesizes from the individual amino acids the particular proteins which constitute its tissue.

By studying the action of the proteolytic enzymes which can be isolated from living tissue, it has been possible to obtain mixtures of substances which are intermediate between proteins and amino acids. These are known as **proteoses** and **peptones**. They are water-soluble materials; unlike most proteins they do not coagulate on heating. Their molecules must be a great deal smaller than those of the proteins but they are still complex substances.



The acid chlorides of the amino acids themselves are very difficult to prepare but this may be accomplished in a few instances by the action of phosphorus pentachloride and acetyl chloride on the amino acid. These acid chlorides will react with an amino acid, producing a dipeptide, or with a dipeptide, forming a tripeptide. An example of the latter reaction would be the preparation of glycyl-glycyl-glycine.



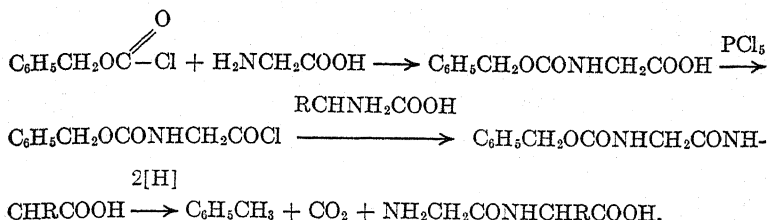
It is evident that by repeating either of these two methods a molecule may be constructed containing many of the simple amino acid residues. However, the preparation of acid chlorides of amino acids containing other reactive groups, such as hydroxyl, is not possible and, in general, these methods are not applicable to the synthesis of polypeptides composed of acids of groups B and C (p. 570) or even the more complicated acids of group A.

Since Fischer's work, numerous special procedures have been devised for synthesizing peptides from certain of the more complicated amino acids. In general, methods have been sought of protecting the reactive groups in the molecule, including the alpha amino group, before the acid is treated with such a reagent as phosphorus pentachloride to form the acid chloride. The difficulty has been to then remove these protecting groups after the peptide has been synthesized without hydrolyzing the peptide link. The use of the **carbobenzyloxy group**,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCO}-$  (also called a **carbobenzoxy group**) has recently been introduced with great success. If benzyl alcohol is treated with phosgene under suitable conditions, the benzyl ester of chloroformic acid (p. 247) is formed,

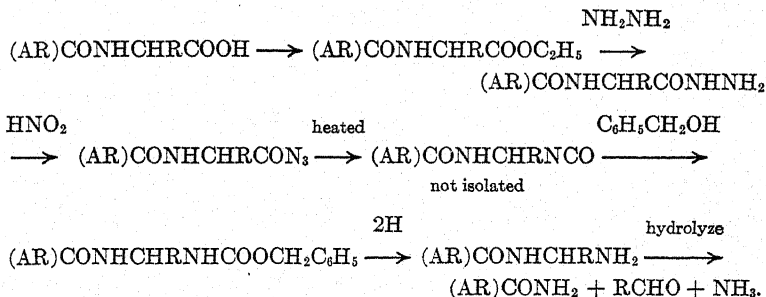
O  
||  
 $\text{C}_6\text{H}_5\text{CH}_2\text{OC}-\text{Cl}$

This substance is in a sense both an ester and an acid chloride. It readily reacts with amino compounds replacing one hydrogen atom by the  $\text{C}_6\text{H}_5\text{CH}_2\text{OCO}-$  group. This protecting group may be removed when desired by catalytic hydrogenation or by reduction with metallic sodium in liquid ammonia. (This latter method also removes benzyl groups,  $\text{C}_6\text{H}_5\text{CH}_2-$  which may have been introduced to protect hydroxyl or mercaptan groups during peptide syn-

thesis.) A simple example of the use of the carbobenzyloxy group is as follows:



**Degradation of Peptide Chain.** Polypeptides are hydrolyzed to the constituent amino acid by heating with acids or by the action of various enzymes. Complete hydrolysis, although it reveals the amount of each amino acid combined in the peptide, obviously gives no information as to the order in which the components are linked. Thus leucyl-glycyl-alanine and glycyl-alanyl-leucine would yield identical mixtures of amino acids on hydrolysis. Stepwise hydrolysis is possible in certain instances by means of enzymes and important information can sometimes be obtained in this manner. A general procedure has been developed taking advantage of the Curtius reaction of the acid azides (p. 255) and of the cleavage of the carbobenzyloxy linkage by reduction. Each constituent amino acid residue can be removed from a peptide chain step by step in the form of the *corresponding aldehyde* (which is identified by the usual method). The fundamental reactions may be illustrated by letting (AR)CONHCHRCOOH stand for a polypeptide whose terminal constituent on one end is the amino acid RCHNH<sub>2</sub>COOH and (AR) the rest of the molecule.



In practice the terminal free amino group of the peptide is first converted into the C<sub>6</sub>H<sub>5</sub>CONH- group by treating the peptide with benzoyl chloride; other reactive groups would have to be protected also. The final cleavage depends

on the fact that a compound of the type  $\begin{array}{c} \text{NH}_2 \\ | \\ \text{RCH} \\ | \\ \text{NHCOR} \end{array}$  on hydrolysis would

yield a compound with two amino groups on the same carbon atom. Such substances, like those which might have two hydroxyl groups (p. 125), are unstable and in aqueous solution yield ammonia and an aldehyde. The other product of the reaction, an acid amide, may be converted into the azide required for the next step of the degradation by treating with hydrazine (replacement of  $-NH_2$  by  $-NHNH_2$ ) followed by nitrous acid.

Degradation of glycyl-alanyl-leucine by this procedure yields in the first step, isovaleric aldehyde and in the second, acetaldehyde and glycine (as the benzoyl compound).

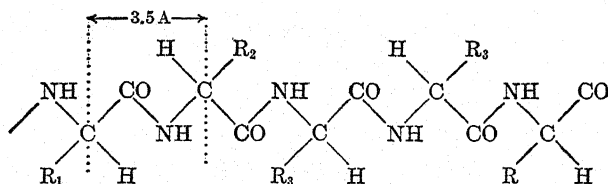
### PROTEINS

In considering the structure of the proteins, it is convenient to recognize at the outset two large subdivisions of this great class of naturally occurring compounds. In one group we may place those fibrous insoluble proteins such as constitute the major part of wool, hair, silk, and the connective tissues of animals. In the other we may place all the other plant and animal proteins which are soluble without decomposition in either water, water-alcohol mixtures, dilute aqueous salt solutions, or dilute aqueous alkali or acid. The substances in both classes are clearly of very high molecular weight and on hydrolysis are completely broken down to a mixture of amino acids.

The differentiation of proteins into these two groups corresponds, as we shall see, not only to very different physical and chemical properties (*e.g.*, solubility) but to a somewhat different composition and to a different shape of the molecule.

**Keratin and Fibroin.** Hair and silk are nearly pure proteins; the former is known as keratin, the latter as fibroin. They dissolve only in strong acids and bases and are at least partially decomposed under these conditions. They are insoluble in all of the ordinary solvents and the usual methods of organic chemistry, therefore, are not available for investigating their structure. The use of physical methods has, however, thrown much light on the structure of these proteins. By using essentially the same technique as is employed in determining the structure of crystals by X-ray diffraction, it was shown that fibroin and keratin molecules contain a recurring pattern of atomic centers. These, we have every reason to believe, are the characteristic recurring links of the peptide chain. The keratin and fibroin molecules are thus composed of very long peptide chains just as the cellulose molecule

(p. 318) is composed of a long chain of connected cellobiose molecules. Certain ones of these protein fibers show two different X-ray patterns according to whether they are stretched or unstretched. The distances between recurring centers is much greater in the stretched form. This indicates that in the normal fiber the chain is somewhat coiled by virtue of attraction, perhaps, between alternating CO and NH groups. This would bring the side chains represented by  $R_1R_2$  (below) nearer together. It is the recurring pattern of these branches which produces the characteristic X-ray diffraction. The distance between CHR groups in



Fragment of keratin molecule in stretched fibre.

the extended chain is 3.5Å according to the X-ray measurement. This is practically identical with the distance calculated from the known internuclear distances of the normal C—C (1.54Å) and the C—N links (approx. 1.4Å), assuming a valence angle of both links of  $109^\circ 28'$ .

**Composition of Fibrous Proteins.** The amino acids obtained from the hydrolysis of the inert insoluble proteins such as silk, hair, wool, and hide are largely those of group A (p. 569). This means that the side chains ( $R_1$ ,  $R_2$ ,  $R_3$ , etc.) extending away from the polypeptide chain are chemically inert. Fibroin (silk) is composed almost entirely of glycine, alanine, and tyrosine. The amino acids of group C are absent and only very small quantities of arginine and lysine (class B) are present. Keratin from wool contains a larger percentage of the basic amino acids. On hydrolysis of keratin (wool), glutamic acid (class C) is also formed in considerable amounts, but so is free ammonia. This indicates that almost all of the COOH groups in the side chain of *D*-glutamic acid are present as neutral amide groups  $-\text{CONH}_2$ . The insolubility of the fibrous proteins in dilute aqueous acids and bases is thus explained both by their high molecular weight and by the

absence of any large number of acid or basic groups in the side chains.

**Classification of Other Proteins.** Leaving aside the inert proteins we have just been considering, we may classify the others by their solubility relations. This is a rough empirical but useful classification, and we shall see that it is not unrelated to the preponderance of one type of amino acid or another in the molecule.

1. **Albumins:** Soluble in water and dilute salt solutions. **Egg albumin** (white of egg) is an example.

2. **Globulins:** Insoluble in water but soluble in dilute solutions of neutral salts. The vegetable protein, **edestin** (from hemp seed), and the animal protein, **serum globulin** (in the blood serum), are two examples of this class.

3. **Glutelins:** Insoluble in water or dilute neutral salt solutions. Soluble in alkaline or acid solution. **Glutenin**, which occurs in wheat, is a representative.

4. **Prolamines:** Insoluble in water or dilute salt solutions. Soluble in 80 per cent alcohol. All the representatives of this class are vegetable proteins. **Zein** occurs in corn, **gliadin** in wheat.

5. **Histones and Protamines:** Basic proteins, soluble in water and acids. The two classes are usually separated on the basis of the insolubility of histones in ammonia. Protamines occur in ripe fish sperm.

In some classifications, fibroin, keratin, and the other fibrous proteins are classified as a sixth group, **albuminoids**. The name which suggests some relation to the albumins is, however, unfortunate.

**Acid and Basic Properties.** A large number of the proteins are amphoteric substances; they combine with acids or bases forming water-soluble salts. This process is strictly reversible unless very strong acid or alkali is employed, in which case the protein may be altered (denatured). The globulins and glutelins which are insoluble in water dissolve in dilute acid or basic solution because of the formation of water-soluble salts. Their behavior is exactly like that of the aminophenols (p. 393).

As in the case of the amino acids, each amphoteric protein will

migrate during electrolysis of the solution to either the anode or cathode, depending on the acidity of the medium. The **isoelectric point** at which no migration takes place is an important characteristic of each protein.

In general, proteins are least soluble *near* their isoelectric point. Therefore, in "salting out" proteins or precipitating water-insoluble proteins, care is taken to bring the acidity of the solution to the proper value. For egg albumin this is a hydrogen ion concentration of  $15 \times 10^{-6}$ ; for hemoglobin,  $2 \times 10^{-7}$ . It will be recalled that pure water has a hydrogen ion concentration of  $1 \times 10^{-7}$ .

In addition to the amphoteric proteins, there are others in which either the acid or basic properties are especially pronounced. The **protamines** which occur in fish sperm are an example of a basic protein. **Zein**, the protein of corn, is just the reverse; it reacts with bases but not with acids. For this reason, zein dissolves in alkaline solution but not in acids.

**The Significance of Acid and Basic Amino Acids.** If the protein molecules were composed only of the amino acids listed in class A of our tabulation (p. 569), they would be neutral substances without acid or basic properties. An approach to this condition is found in the case of keratin and fibroin. If a large proportion of the constituent amino acids were of class C, the side chains would carry carboxyl groups. Unless these groups were present as amides (as in the case of wool), the protein should have the capacity of forming salts with bases. The presence of a large proportion of basic amino acids (group B) in a protein should endow it with the property to form salts with acids. If, however, representatives of both class B and C were present in goodly number, the large molecule should be amphoteric. This is the case with egg albumin, for example, which contains about 10 per cent of basic amino acids and about 15 per cent of acidic amino acids (class C). An examination of the amino acids formed by hydrolysis has shown that *the acid and base binding capacity of different proteins is determined by the nature of the amino acids of which their molecules are composed.*

A few examples will make this clear. Zein which has no basic properties contains an extremely small amount of basic amino acids, but the protamines, which are basic, yield on hydrolysis large amounts of amino acids with basic groups (class B). Quanti-

tative experiments have shown that casein neutralizes twice as much sodium hydroxide as it does hydrochloric acid. The composition of this amphoteric protein corresponds closely with this relationship; it yields about twice as many molecules of the acid amino acids (class C) as basic amino acids (class B). Thus the amino acids with extra basic or acid groups are of fundamental importance in determining the behavior of proteins.

**Purification of Proteins.** The method of purifying proteins is based on their solubility in water and in salt solutions. Strangely enough, some proteins which are insoluble in pure water are soluble in dilute salt solutions. These are called **globulins**. All proteins are insoluble in a concentrated salt solution such as saturated ammonium sulfate. Water-soluble proteins, therefore, may be "salted out" by the addition of solid ammonium sulfate. The precipitate redissolves on treatment with pure water. A number of proteins have been obtained in the crystalline condition by careful regulation of the hydrogen ion and salt concentration of saturated solutions. The recrystallization of such proteins is the best method of purification. The crystals are kept moist throughout the procedure as drying alters most soluble proteins to some extent.

There are proteins found in grain which are soluble in an 80 per cent mixture of alcohol and water but are insoluble in both pure water and pure alcohol; they are known as **prolamines**.

**Irreversible Precipitation of Proteins.** The reversible precipitation just mentioned is very different from the *irreversible precipitation* of proteins which is brought about by a number of reagents such as **trichloroacetic acid**, **tannic acid**, **picric acid**, **concentrated nitric acid**, and **phosphotungstic acid**. The mercury, lead, and copper salts of proteins precipitate when soluble salts of these metals are added to protein solutions. This is also essentially an irreversible process as the original protein can not be obtained from these precipitates. The precipitation of proteins by such reagents is useful in testing for proteins or removing them from a solution but can not be used in purification as the process in some way alters the material.

The majority of water-soluble proteins are precipitated when their solutions are heated. This process is irreversible. The

"cooking" of white of egg is a common example of the heat coagulation of a protein.

**Molecular Weights of Proteins.** Even the water-soluble proteins are substances of very high molecular weight. The usual direct methods of determining molecular weight, for example, by the observation of the freezing point of solutions of known concentration can not be employed. With substances of large molecular weight the depression is too slight to be measured accurately and the presence of even small quantities of inorganic impurities would vitiate the result. Some determinations of the osmotic pressure of protein solutions have given fairly satisfactory information in regard to the molecular weights but the most reliable method depends on the use of the ultra-centrifuge. In this procedure a solution of the substance of high molecular weight is spun at very high speeds. The centrifugal force thus generated moves the dissolved molecules away from the center. While the container is still being rotated at the desired speed the concentration gradient from the center to the outside edge is determined by a photographic method. Knowing the speed, the dimension of the ultra-centrifuge, and the change in concentration of the protein solution throughout the revolving container, it is possible to calculate the molecular weight. Some of the results obtained are given below:

MOLECULAR WEIGHTS OF SOME PROTEINS

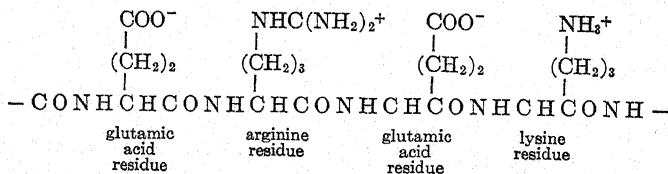
Lactalbumin	17,500	
Gliadin	27,000	
Zein	35,000	
Insulin	38,000	
Egg Albumin	42,000	(By osmotic pressure, 35,000)
Hemoglobin	68,000	(Same value by osmotic pressure)
Serum albumin	68,000	(By osmotic pressure, 75,000)
Serum globulin	167,000	(By osmotic pressure, 175,000)
Phycocyan	272,000	
Edestin	309,000	
Hemocyanin	6,700,000	

In solution the proteins are probably present in more or less spherical globular form. When they are distributed as a thin film, however, on the surface of a liquid, the soluble proteins appear to approach the condition of the fibrous proteins; the molecules then consist of parallel, extended, polypeptide chains.

**Denaturation.** Perhaps the most characteristic property of the soluble proteins is the ease with which they undergo a change known as denaturation. A denaturated protein is less soluble than the normal (or native) protein and it will not crystallize. Drying, treatment with rather concentrated acid or alkali, and the addition of alcohol to an aqueous solution denature many proteins; a concentrated solution of urea is also an effective agent for bringing about denaturation. The ease with which many proteins are thus altered makes the manipulation of this class of substances peculiarly difficult. The technique employed is, therefore, quite different from that used with most organic compounds.

The coagulation of protein solutions on heating and the precipitation with many reagents, such as metallic salts and tannic acid, are examples of extreme denaturation. Certain proteins, if denatured by relatively mild reagents, can be slowly restored to the native state by dissolving in alkali and then adjusting the hydrogen ion concentration to a proper value. Measurements of the molecular weight by the osmotic pressure method indicate that in a number of instances there is no change in the molecular weight on denaturation. With a few proteins of very high molecular weight, denaturation appears to involve a dissociation of the molecule into as many as six parts.

**Structure of Soluble Proteins.** The presence of a considerable number of basic and acid amino acids (groups B and C) in a protein molecule must mean that many side chains carry electric charges. The acidic and basic groups must interact to form salts by transfer of a proton. Thus, a hypothetical fragment of a protein molecule containing considerable amounts of lysine, arginine, and glutamic acid might be represented as follows:



The existence of many electric dipoles on a chain must modify enormously the forces involved in the arrangement of the chain in

three dimensions. Furthermore, a large molecule carrying these charges has unusual properties. A solution of a protein has an enormously high dielectric constant. This fact is of great significance not only to protein chemistry but to biology. Some of the larger protein molecules may be aggregates of several molecules held together by electrostatic charges. In some cases, the apparent molecular weight is a function of the concentration and the hydrogen ion concentration.

It seems probable that in the globular form in solution the polypeptide chain is folded into some network. Whether, in the folding of a chain into a globular form, real covalence forces are involved, is still a matter of discussion. It has been suggested that six-membered rings are formed by cyclization of the CO group with the NH group twice removed along the chain. The dissolved protein molecule is also probably heavily hydrated.

Denaturation seems to involve the change of an ordered three-dimensional pattern of the native globular protein in the direction of a more random arrangement of the polypeptide links. Some valence bonds may be broken in this process but no drastic cleavage of the polypeptide chain is involved.

Although synthetic work established the fact that the proteoses are polypeptides (p. 577), the difference in behavior and molecular weight between these compounds and proteins led some chemists to believe that other types of linkages were characteristic of proteins. All the evidence accumulated in recent years, however, indicates that the polypeptide chain is the essential element in the structure of even the giant molecules of a protein. It has been established, for example, that some of the enzymes which hydrolyze native proteins are also effective in hydrolyzing synthetic peptides. They attack preferentially the interior peptide links. Thus, the enzymatic hydrolysis of a protein seems to involve only the hydrolysis of the  $\text{—CONH—}$  bond.

**Arrangement of Amino Acid Residues.** The properties of a given protein must depend to a large extent not only on the number and kind of amino acids of which the molecule is composed but also on the order in which the residues are linked together. To attempt to determine this order by step by step degradation would seem a hopeless task for a molecule containing many hundreds of such components. A study of the number of molecules of each kind of amino acid produced by the hydrolysis of one molecule of a given protein

has yielded, however, some striking information. For example, an analysis of the hydrolysis products obtained from hemoglobin shows the number of grams of each of eight amino acids obtained from 100 grams of protein; from these figures the relative number of residues in the protein can be calculated. Thus, in the hemoglobins from cattle, horse, and dog, there are three times as many lysine residues as arginine.

The ratio of cysteine to lysine, however, is different in the hemoglobin from each species. Although no complete analysis of any protein hydrolysate has been accomplished, in a number of instances the analytical values for half a dozen or more of the components are known with considerable accuracy. From the percentage of a given amino acid in the hydrolysis product of a protein, one may calculate the ratio of the number of moles of this *particular* acid to the total number of moles of *all* the acids from a given weight of protein. The smaller this ratio, the more frequently the acid in question must occur in the molecule. The reciprocal of this ratio, indeed, is a measure of the *frequency* with which this amino acid occurs. To illustrate by a simple example, if every fourth residue in a chain were glycine, the ratio of glycine to all the amino acids would be 1 : 4 and the frequency of occurrence of this particular amino acid would be 4. On the other hand, if, in this hypothetical case, a glycine residue were a less frequent member of the chain, the ratio might be 1 : 18 and the frequency would then be 18. For example, calculating such frequencies for eight amino acid residues of hemoglobin from the analytical data showed that lysine occurred the most often (frequency of 16) and cysteine the least (frequency of 192). Histidine and aspartic acid both had a frequency of 18. If we assume that the whole molecule is a continuous polypeptide chain with a regular sequence of amino acid residues, then clearly the chain must be at least 192 links long in order to contain one cysteine component. But such a length would not accommodate 18 histidine residues as 192 is not a multiple of 18. 576 ( $3 \times 192$ ) is a multiple of 18, however. Therefore the shortest chain compatible with the results would be one composed of 576 components. In such a molecule the number of actual units of cysteine would be 3, of histidine 32, and of lysine 36. The molecular weight would be  $576 \times 115.5$  (the average molecular weight of all the amino acid residues) = 66,500, to which must be added the iron and the colored prosthetic group (p. 589) giving a value of 69,000. This is very close to that determined by osmotic pressure and the ultra-centrifuge. The agreement may be taken as confirmation of this picture of the protein molecule.

The examination of a number of proteins suggests that the frequency of occurrence of each amino acid in a particular protein may be expressed as a power of 2 and a power of 3. Thus, the frequency of lysine in cattle hemoglobin is  $2^4 \times 3^0$ , of histidine  $2^1 \times 3^2$ . The frequency of a given amino acid may be quite different in different proteins but it appears from the cases thus far examined to be *always a number which can be expressed as  $2^n \times 3^m$  where  $n$  and  $m$  are zero or small whole numbers*. The fundamental reason for this empirical numerical relationship is not clear. Presumably the explanation of the regularity found by comparing the frequencies in different proteins must be

sought in terms of the mechanism by which proteins are built up in plant and animal cells. It may be not unrelated to the facts that all starches and cellulose have a common building unit and that in the structure of a variety of natural substances, the isoprene residue forms a regular pattern.

An inspection of the molecular weights of a great number of proteins, in the light of the stoichiometric laws of protein composition, suggests that the living cell may synthesize protein molecules containing 144 ( $2^4 \times 3^2$ ) units or some simple multiple of this unit such as 288, 576, 1152, etc. *but none in between*. This would mean that the proteins should fall into groups differing from each other greatly in their molecular weights. Each member of the group would have a molecular weight approximating that of the mean molecular weight of the residues of all types of amino acids (about 120) times the number of units. Thus  $144 \times 120 = 17,300$ ;  $288 \times 120 = 34,500$ , etc. The actual molecular weight of the residues differs from acid to acid; thus, the molecular weight of the residue of glycine is 57 and of tryptophane, 186. Therefore, the exact molecular weight would depend on the kind of amino acids present as well as the number of units. The facts thus far known support this view. Proteins do, indeed, fall into classes accordingly, as their molecular weights are *approximately* 17,500, 35,000, 52,500, etc.

**Conjugated Proteins.** A totally different method of classifying proteins from the one we have been using is sometimes employed. Proteins are divided into simple proteins which yield only amino acids on hydrolysis and the others called conjugated proteins in which some other component is linked to the protein. The non-protein portion is called a **prosthetic group**. If the group confers color on the protein as in the case of hemoglobin and the colored proteins present in algae (**phycocyan**), the protein may be known as a **chromoprotein**. If the prosthetic group is a carbohydrate the substance is a **glucoprotein**. Glucoproteins are found in mucous secretion. Casein (from milk) is often classed as a **phosphoprotein** as the prosthetic group contains phosphoric acid. The **nucleoproteins** contain a nucleic acid (p. 523) residue linked to the protein molecule. When the prosthetic group is colored it is easily recognized. In some cases, as with hemoglobin, it is joined to the protein by some linkage that may be attacked by certain reagents without hydrolyzing the protein. If the prosthetic group is joined by an amide linkage, it may not be possible to separate it from the rest of the molecule without drastic decomposition of the protein. There may be a number of prosthetic groups (*i.e.*, residues other than amino acids) which have not yet been isolated and identified from well-known proteins.

**Macromolecules and Filterable Viruses.** Hemocyanin, the blue protein which carries oxygen in the horseshoe crab and the lobster, has an apparent molecular weight of 6,700,000. (The blue color is due to a copper atom bound to the protein.) The molecule of this protein is so large as to deserve the name of a macromolecule which has sometimes been applied to all protein molecules. Nucleoproteins of very high molecular weight (approximately 17 million) have been isolated in crystalline condition from the juice of plants infected with certain diseases such as the mosaic disease of tobacco. They are known as the **virus proteins** and are the active agents in transmitting the disease from one plant to another. Because of their high molecular weight, they may be concentrated by the use of the ultra-centrifuge. In general their purification by crystallization follows the usual procedures of protein chemistry. When denatured or slightly modified by the action of reagents, the protein loses its power of inducing the disease. A study of the physical properties of the protein solution indicates that the molecules are rod-shaped, the polypeptide chain being perhaps coiled as in a long spiral chain.

A great number of diseases of plants and animals are transmitted by what are known as filterable viruses. Many of these viruses pass through filters which hold back even the smallest bacteria. In the case of tobacco mosaic disease and certain other plant diseases, the active agent of the filterable virus is a protein. Whether or not all filterable viruses are proteins has not yet been determined. Unlike bacteria and almost all infectious organisms, filterable viruses do not multiply away from the living cells of the plant or animal they infect. Whether in the host filterable viruses increase much as do bacteria or whether they are products of the metabolism of the infected cells is still undetermined and is a subject of much discussion. The smaller virus proteins are of the same order of size as the largest hemocyanin molecule (diameter of about 25  $m\mu$  (250A) if the molecule is spherical). The largest, however (*e.g.*, vaccine virus), corresponds in size (diameter = 150–175  $m\mu$ ) to organisms which have been long recognized as living and which can multiply outside a living cell.

**Enzymes.** The living cells of plants and animals produce a variety of catalysts known as enzymes. We have already had occasion to refer to a number of such substances which can bring about certain specific transformations such as the fermentation of sugar to alcohol (p. 15) and the hydrolysis of glucosides (p. 313). Until a few years ago enzymes were known only in the form of extracts prepared from plant or animal material by grinding or crushing the cells and extracting with water or salt solutions (the hydrogen ion concentration is often of the greatest importance). By evaporating such extracts under diminished pressure at room temperature, amorphous powders were obtained which, on dissolving, yielded solutions of high enzymatic activity. Such prepara-

tions are, however, very impure and contain great quantities of inert organic material.

A great step forward was made in the study of enzymes when it was found that certain crystalline proteins could be isolated which had high enzymatic activity. They retained this activity as the purification by crystallization proceeded. More than half a dozen enzymes have now been prepared in the crystalline condition. They include *urease* (p. 250), several protein-splitting enzymes such as *pepsin* and the oxidation enzyme *flavoprotein* (p. 528). Like all proteins these substances are sensitive and easily altered or partially denatured. When this occurs the enzymatic activity disappears. In a few instances this loss of activity can be restored by the same procedure used in reversing the denaturation of proteins. More often the change is irreversible. All enzymes are *thermo-labile*, that is, the activity of the preparation is lost when the solution is heated for a short time to temperatures of 90°–100° C. Enzymes also usually lose their activity when treated with such powerful reagents as strong acids or strong alkalies or oxidizing agents. All these facts taken together with what is known of the enzymes which have been crystallized indicate (but do not prove) that all enzymes are proteins. If this is, indeed, the case, the loss of activity of enzymes is but a special case of the denaturation of proteins.

Enzymes are specific in their action. It will be recalled, for example, that *emulsin* will bring about the hydrolysis of  $\beta$ -glucosides but not of  $\alpha$ , while *maltase* acts in just the reverse manner. The catalytic activity of each enzyme is usually at a maximum at some temperature not greatly above room temperature and at a certain acidity. The concentration of the material which is undergoing the chemical change (*the substrate*) is also often important. In certain cases, the accumulation of the products of the reaction slows down the enzymatic reaction. *Co-enzymes* (or co-ferments) are relatively thermo-stable substances which are essential for the enzymatic action. Thus, calcium (in the ionic form) is a co-enzyme for the clotting of milk by the enzyme *rennin* (conversion of the soluble protein *caseinogen* to the insoluble *casein*). In this instance we have no idea why the calcium ions are necessary. In the series of enzymatic changes involved in the conversion of *glycogen* to lactic acid in muscle tissue, *adenyl pyrophosphate* is a

co-enzyme. In this instance, we know the role of the co-enzyme. It seems to transfer a molecule of phosphoric acid to the carbohydrate (p. 315).

It has been often stated that the enzyme and substrate are related as a key to a lock. One can imagine that certain specific linkages must be present in both enzyme and substrate in order to allow the two substances to interact. Whether the interaction involves the formation of a chemical compound or is in the nature of adsorption is still an open question. Why the substrate undergoes chemical change after combination with or adsorption on the enzyme is far from clear. In a few instances, of which flavoprotein is the best example, the enzyme contains a prosthetic group and the function of this group can be understood. In such a case, the protein may be thought of as a carrier, but one essential for the action of the enzyme. The enzyme which decomposes hydrogen peroxide (catalase) and at least one other oxidizing enzyme appear to have definite prosthetic groups. In the case of the hydrolytic enzymes no prosthetic groups have been as yet identified and the picture of the action of the enzymes is much less definite.

The table opposite summarizes some important classes of enzymes. Those obtained in a crystalline condition are noted by asterisks; the others have been isolated as impure extracts.

**Qualitative Tests for Proteins.** A large number of qualitative tests which serve to identify the various classes of proteins are known. Some tests are given by all proteins, others by proteins containing certain amino acids.

**Biuret Reaction.** This reaction is characteristic of all proteins, peptones and certain non-protein materials which have two  $\text{NH}_2$  groups attached to different atoms. The name of the test arises from the fact that **biuret**,  $\text{NH}_2\text{CONHCONH}_2$ , gives the test. Biuret is formed on heating urea. When a protein solution is mixed with potassium hydroxide and a few drops of copper sulfate solution is added, a pinkish violet color is produced if the test is positive.

**Heller's Ring Test.** The precipitation of albumin with nitric acid is used as a test for this material in urine. The urine is placed in a test tube and concentrated nitric acid carefully added. At the zone between the two liquids, a cloud of precipitated albumen appears if the protein is present.

**Millon's Reaction.** In this test, the solid protein is warmed with a little Millon's reagent (a solution of mercuric nitrate in dilute nitric acid); a yellow or white color changing to red on heating indicates protein. The test is given by those proteins which yield *tyrosine* on hydrolysis and by non-protein substances containing the group  $-\text{C}_6\text{H}_4\text{OH}$ .

**Xanthoproteic Reaction.** Concentrated nitric acid produces a yellow color when it acts on any protein material containing an amino acid with a phenyl group. The yellow color turns orange with ammonium hydroxide.

## THE MORE IMPORTANT CLASSES OF ENZYMES

NAME	SUBSTRATE	PRODUCTS FORMED	COMMON SOURCES	PREVIOUS REFERENCE IN THIS BOOK
<i>A. Hydrolyzing Enzymes</i>				
1. <i>Carbohydrases</i>				
Diaxase or amylase	starch	maltose	yeast, saliva, pancreatic juice	p. 16
Invertase or saccharase	cane sugar	glucose and fructose	yeast, leaves of many plants, mammalian gut	p. 311
Emulsin or $\beta$ glucosidase	amygdalin, $\beta$ glucosides	glucose and OH compound	seeds of plants (almond)	p. 314
Maltase	maltose, $\alpha$ methyl gluco- side	glucose, glucose + $\text{CH}_3\text{OH}$	malt, yeast, human gut	p. 314
2. <i>Esterases</i>				
Lipase	esters of fatty acids	acid and alcohol	liver, pancreas, stomach	
Phosphatase	nucleotides	nucleosides + $\text{H}_3\text{PO}_4$	mammalian gut	
3. <i>Proteases and Peptidases</i>				
*Pepsin	proteins	proteoses and peptones	stomach	p. 576
*Trypsin	proteins, peptones	peptides	stomach	p. 576
Aminopoly- peptidase	peptides	simpler peptides	pancreas, intestine	
4. <i>Deaminases</i>				
*Urease	urea	ammonium carbonate	soya bean	p. 250
Arginase	arginine	ornithine + urea	liver	p. 574
<i>B. Oxidizing and Reducing Enzymes</i>				
*Catalase	$\text{H}_2\text{O}_2$	$\text{H}_2\text{O} + \text{O}_2$	liver, blood	
Lactic dehy- drogenase	lactic acid	pyruvic acid	tissues	p. 315
Succinic dehydro- genase	succinic acid	fumaric acid	muscle, bacteria	
Zymase (probably a mixture)	glucose	$\text{CO}_2 +$ $\text{C}_2\text{H}_5\text{OH}$	yeast	p. 15
*Flavoprotein (Warburg's yellow en- zyme)		involved with other enzymes and co-enzymes in complete oxidation of sugars by oxygen		p. 528
*Cytochrome		involved in cell oxidations		p. 529

**Protein Hormones.** Two hormones which are proteins and whose action has been much studied are thyroglobulin and insulin. In the case of the former, the hormone action is closely associated with certain amino acids which carry iodine, namely, thyroxine and iodogorgoic acid (nos. 14 and 15 on p. 570). Indeed, thyroxine itself is often spoken of as a hormone. Its structure has been established by degradation and synthesis. It is now synthesized industrially. Since this compound contains a large amount of iodine, a supply of iodides is necessary if an animal is to produce this hormone. Disorders of the thyroid gland occur in some localities because of lack of iodides in the water and food supply. Thyroxine and thyroid extract are used in the treatment of such pathological conditions.

Insulin is a hormone secreted by the ductless glands of the pancreas. It is essential for the proper combustion of carbohydrates in the animal body. The absence of this hormone produces diabetes. It can be obtained in a crystalline condition, and its molecular weight is approximately 35,000. Unlike thyroglobulin, no uniquely characteristic amino acid has been isolated from it nor does it appear to contain a prosthetic group. It has been suggested that certain of the amino acids in the molecule are particularly important in the action of this hormone but no clear picture of the physiological action of this hormone has been as yet obtained.

### QUESTIONS AND PROBLEMS

1. Write structural formulas for: three monoamino monobasic acids, two diamino monobasic acids; and two monoamino dibasic acids.
2. Compare the physical and chemical properties of the substances mentioned in question 1.
3. Name three common substances of widely different properties which are proteins. What characteristics have they in common? What economic importance has each of these substances and on what properties does the economic importance of each depend?
4. If a water-insoluble protein yielded chiefly dibasic monoamino acids on hydrolysis, what would you predict in regard to its solubility in dilute acids and alkalies?
5. Outline the steps in three methods of preparing *d*, *L*-alanine.
6. Write equations showing two methods of synthesizing polypeptides. What conclusions in regard to the structure of peptones and proteins may be drawn from Fischer's work?
7. When a formaldehyde solution is added to that of an amino acid, a reaction occurs and the resulting water-soluble acid has no basic properties. What reaction do you think probably takes place? The product can be titrated like acetic acid with sodium hydroxide and an indicator. How could you take advantage of this fact in determining the amount of an amino acid in a solution also containing polypeptides?
8. Devise two methods for following the course of the hydrolysis of a water-soluble protein to the component amino acids. Assume the investigator is particularly anxious to determine when all the peptide links have been broken by hydrolysis.

9. Outline the steps in the synthesis of alanyl-glycyl-glycine from the component amino acids using the carbobenzyloxy method.

10. Outline a possible synthesis of tyrosyl cysteine using the benzyl group (introduced by the use of benzyl chloride) to protect OH and SH groups and the carbobenzyloxy group to protect the amino group.

11. Define the terms: prosthetic group, enzyme, filterable virus, denaturation, iso-electric point, prolamine, protamine, conjugated protein.

12. With the aid of structural formulas outline the course of the formation of urea from carbon dioxide and ammonia in the animal body.

13. Gelatine is a partially hydrolyzed fibrous protein prepared commercially from hides. How would you distinguish it from a gelatinous carbohydrate, agar-agar? How would you determine the amount of gelatine in a mixture of the two?

14. Compare and contrast the phenomena of: (a) cooking of an egg; (b) destroying of bacteria by sterilization; (c) inactivation of an enzyme by heating.

15. Outline a possible scheme to account for the formation of skatole as a decomposition product of proteins.

16. How do you account for the stability (resistance toward hydrolysis) of the  $C=NH$  in creatine and arginine? Arginine and histidine contain one relative strong basic group. What is the explanation in each case?

## CHAPTER XXXII

### PLANT AND ANIMAL PIGMENTS

The ultimate source of all organic compounds is the plant kingdom. The *green* plants synthesize from inorganic material a host of complex materials. The primary substances are the carbohydrates and the amino acids or proteins; from them all other classes of material are derived. All living things contain carbohydrates and proteins, but there is considerable specialization in regard to the formation of secondary substances. As we have seen, some materials of great interest are produced in appreciable amounts in only a few species of plants (for example, rubber and indigo). A summary of the synthesis of organic compounds by green plants is outlined below.

**Photosynthesis.** The organic material of green plants is synthesized from inorganic material by means of the energy of sun-

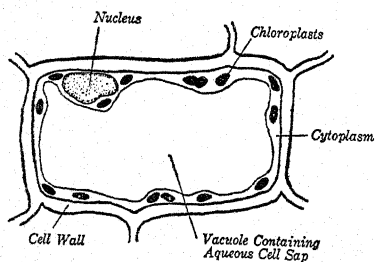


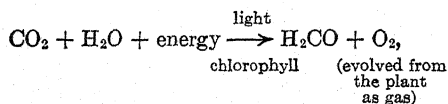
Fig. 35. Diagram of cross section of typical cell of a green leaf.

light absorbed by the green coloring material. This process is known as *photosynthesis*. It takes place in those portions of the protoplasm which contain the coloring material; these are known as the **chloroplasts** (see Fig. 35). The coloring materials present in chloroplasts (chloroplast pigments) are four in number: chlorophyll *a*, chlorophyll *b*, carotene, and xanthophyll. The first two are green, the last two yellow. Almost all green plants contain all four pigments; at least chlorophyll *a* is essential for the process of photosynthesis and, perhaps, all four are needed. With a few unimportant exceptions all the organic material in the world originates by a process of photosynthesis.

# SYNTHESES OF ORGANIC COMPOUNDS IN GREEN PLANTS

RAW MATERIALS	PRIMARY PRODUCTS	THE MORE IMPORTANT SECONDARY SUBSTANCES	
		(a) MOLECULAR WEIGHT LESS THAN 1000	(b) MATERIALS OF HIGH MOLECULAR WEIGHT
$\text{CO}_2$ $\text{H}_2\text{O}$ Inorganic Nitrogen Compounds	<div>             Sunlight              or              chloroplast pigments           </div> <div>             Sugars              Amino-Acids              ↓ ↑              Reserve Materials           </div> <div>             Proteins,              Fats, and              Oils           </div> <div>             Polysaccharides              (e.g., starch),              hemicelluloses           </div>	<div>             Polyene pigments              Aliphatic acids, alcohols              Terpenes              Sterols and related substances              Waxes              Phosphatides (e.g., lecithin)              Inositol              Aromatic hydroxy acids              Hydroxy compounds as glycosides              (Phenols, complex alcohols)              Volatile aldehydes, alcohols, esters, ethers              (In essential oils with terpenes)              Alkaloids              Pyrrole pigments              Anthocyan pigments              Nucleic acids           </div>	Cellulose Hemicelluloses, gums, pectins Resins Rubber Tannins Lignins

The mechanism of photosynthesis is still unknown in spite of many years of investigation by biologists and chemists. The energy required for the reduction of carbon dioxide to sugar is obtained by the absorption of light by the chloroplast pigments. But the way in which this absorbed energy brings about the process of photosynthesis is still uncertain, though a number of attractive hypotheses have been suggested. Most of these hypotheses assume that formaldehyde is the first product in photosynthesis, and that this polymerizes to glucose and fructose (p. 129). However, there is no satisfactory evidence that formaldehyde is the first product of photosynthesis; if it is formed, it undoubtedly at once reacts and is removed.



The summation of the above equations represents the known facts, but many other intermediates between carbon dioxide and sugar might be imagined.

**Plant Pigments.** We shall leave a consideration of the structure of chlorophyll until later in the chapter. The other pigments always found associated with chlorophyll belong to a class of substances known as the **polyene pigments**. A number of other yellow or red pigments belong to this same class, and the similarity to carotene has suggested the name **carotenoid** for the class. Carotene,  $\text{C}_{40}\text{H}_{56}$ , is a highly unsaturated hydrocarbon; it contains 11 double bonds arranged in a conjugated system and two alicyclic rings. The other polyene pigments are either highly unsaturated hydrocarbons or alcohols or acids derived from such hydrocarbons. They are insoluble in water, acids, or alkali (with the exception of those which are acids), but are soluble in chloroform and ether, and are often obtained with the waxes and fats in the extraction of tissues. Because of their highly unsaturated nature, many of them are easily oxidized by atmospheric oxygen; all of them may be hydrogenated (by hydrogen and a catalyst) to saturated com-

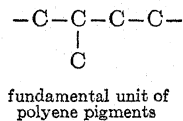
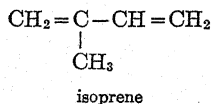
pounds which are colorless. The more important members of the class are given in the accompanying table.

COMPOUNDS CONTAINING A POLY-ISOPRENE SKELETON

NAME	COLOR	MOLEC- ULAR FORMULA	NO. OF C <sub>5</sub> UNITS	NO. OF DOUBLE BONDS	NO. OF ALI- CYCLIC RINGS	OCCURRENCE
Isoprene	none	C <sub>5</sub> H <sub>8</sub>	1	2	0	
Geraniol	none	C <sub>10</sub> H <sub>18</sub> O	2	2	0	essential oils
Limonene	none	C <sub>10</sub> H <sub>16</sub>	2	2	1	essential oils
Farnesol	none	C <sub>15</sub> H <sub>26</sub> O	3	3	0	essential oils
*Crocetin	yellow	C <sub>20</sub> H <sub>24</sub> O <sub>4</sub>	4	7	0	saffron
Squalene	none	C <sub>30</sub> H <sub>50</sub>	6	6	0	shark oil
*Capsanthin	red	C <sub>35</sub> H <sub>50</sub> O <sub>3</sub>	7	?	1 or 2	paprika
*Lycopene	red	C <sub>40</sub> H <sub>56</sub>	8	13	0	tomatoes
*Carotene (α and β)	red	C <sub>40</sub> H <sub>56</sub>	8	11	2	carrots and leaves
Carotene-γ	red	C <sub>40</sub> H <sub>56</sub>	8	12	1	carrots
Cryptoxanthine	red	C <sub>40</sub> H <sub>56</sub> O	8	11	2	yellow corn
*Xanthophyll	yellow	C <sub>40</sub> H <sub>56</sub> O <sub>2</sub>	8	11	2	leaves

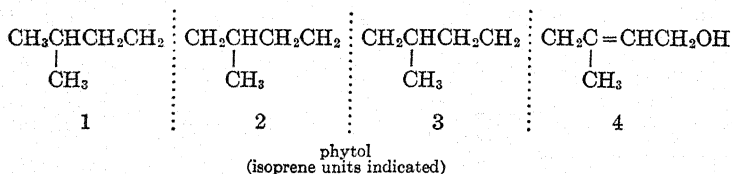
\* Indicates the compound is classified as a polyene pigment.

**Relation to Isoprene.** The fundamental unit of the polyene pigments seems to be the skeleton of the isoprene molecule:

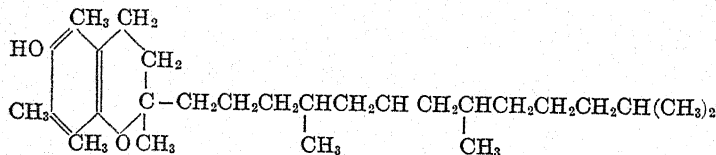


This unit seems to be repeated in a regular fashion in the whole group. It will be recalled that rubber (p. 76) and the terpenes (p. 491) also contain this unit.

**Compounds Related to Polyene Pigments.** Three colorless compounds which have been isolated from plants or animals are closely related to the polyene pigments. They are the alcohol **phytol**,  $C_{20}H_{39}OH$ , which occurs as part of every chlorophyll molecule, a hydrocarbon, **squalene**, which is isolated from the liver oil of sharks, and vitamin A. A consideration of the latter compound will be referred to later. The structure of phytol has been established beyond a shadow of doubt by its synthesis. It is an optically inactive oil of very high boiling point. The carbon skeleton is composed of four isoprene units; there is one double bond and a terminal primary hydroxyl group; the rest of the molecule is saturated. As is evident from the empirical formula, phytol may be regarded as a higher homolog of allyl alcohol ( $C_nH_{2n-1}OH$ ).

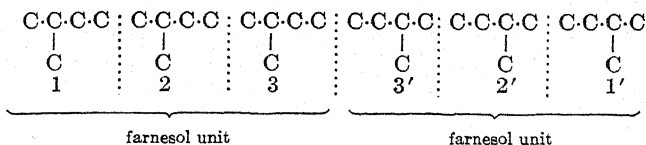


**Vitamin E.** Another biologically important substance containing a polyisoprene chain is **alpha tocopherol**. From preparations of vitamin E (the vitamin whose absence causes sterility in rats) three active compounds have been isolated. The most active of these is alpha tocopherol. It has been synthesized by the condensation of 2, 3, 6-trimethyl-1, 4-hydroquinone and phytol. During this reaction a six-membered, heterocyclic ring containing an oxygen atom becomes fused to the benzene nucleus. The primary hydroxyl group and the double linkage of phytol are involved in the formation of the heterocyclic ring. The structure of  $\alpha$ -tocopherol is as follows:



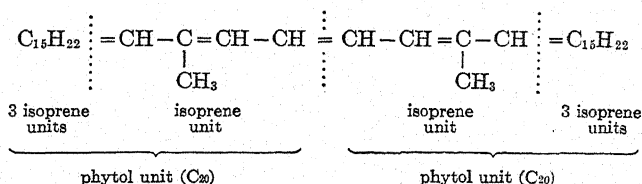
**Squalene**,  $C_{30}H_{50}$ , has six double linkages and no alicyclic rings. Since the double bonds are not conjugated, it is colorless. Its structure has been proved by synthesis. The carbon skeleton consists of two groups of three isoprene units joined to form a symmetrical chain.

**Relation to Open Chain Terpenes.** The carbon skeleton of squalene is as follows:



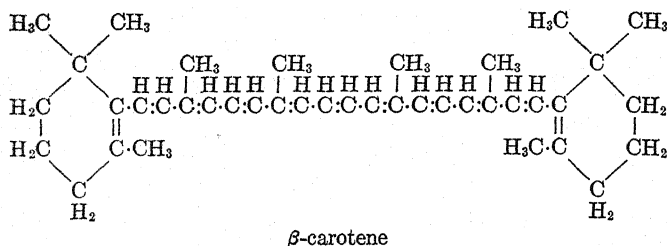
The chief importance of squalene is that its structure has been proved to contain a series of isoprene units arranged in two groups which, in turn, are joined to give a *symmetrical arrangement*. The two units of fifteen carbon atoms in squalene correspond to that present in an open-chain terpene alcohol, **farnesol**, found in certain essential oils. This fact connects the higher members of the polyene series with the lower. There are a number of substances occurring in essential oils which contain the ten-carbon unit formed from two isoprene skeletons (see p. 492) (*e.g.*, 1 + 2 in the squalene formula above). Taking isoprene as a starting point, natural products are known which contain from 1 to 8 isoprene units arranged according to a definite pattern. The state of unsaturation of these compounds differs greatly; some of the substances are acids, some alcohols, some hydrocarbons. The recurrence of the same building unit of five carbon atoms connects them all together, however.

**Structure of Lycopene and Carotene.** In lycopene (also called **lycopin**),  $\text{C}_{40}\text{H}_{56}$ , the red coloring material of tomatoes, the carbon skeleton is composed of eight isoprene units arranged in two groups of four each, each group being like the skeleton of the phytol formula. The two  $\text{C}_{20}\text{H}_{28}$  units are joined so that the central portion of the molecule has *four* carbon atoms between two branching methyl groups. The formula may be written thus:



As the table on p. 599 indicates, there are three isomeric carotenes. Beta and gamma carotenes are optically inactive while alpha carotene is dextrorotatory. The structure of  $\beta$ -carotene

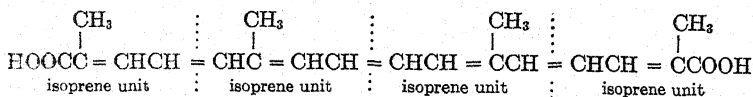
is as follows:



It will be noted that the formula shown above has a symmetrical arrangement of two units of twenty carbon atoms each. As in the case of lycopene and squalene there are *four* carbon atoms between the two atoms which carry the methyl groups in the middle of the formula.

Alpha carotene differs structurally from the beta form in the positions of the double bond in one of the alicyclic rings. In gamma carotene one of the alicyclic rings is open, a new double bond taking the place of the ring. Gamma carotene may be considered as being made up of one half of a  $\beta$ -carotene molecule and one half of a lycopene molecule joined together, having the characteristic four-carbon atom chain in the center.

The yellow pigment of saffron is *crocetin*, a dibasic acid,  $C_{20}H_{24}O_4$ . Its structure has been proved to be as follows:



It will be noted that the four isoprene units are arranged in groups of two; the two groups are joined in a symmetrical arrangement. There are four carbon atoms between the two branching methyl groups in the middle of the formula. A comparison of this formula with that of beta carotene or lycopene shows that it could be formed by the symmetrical removal of ten carbon atoms from *each end* of the larger molecule. It seems probable that it does arise by the oxidation of carotene or lycopene. Probably certain other carotenoids and the colorless squalene also arise by a symmetrical degradation of carotene (or lycopene) by oxidation. Such an origin would account for the occurrence of

$\begin{array}{c} \text{CH}_3 \\ | \\ -\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}- \\ | \\ \text{CH}_3 \end{array}$

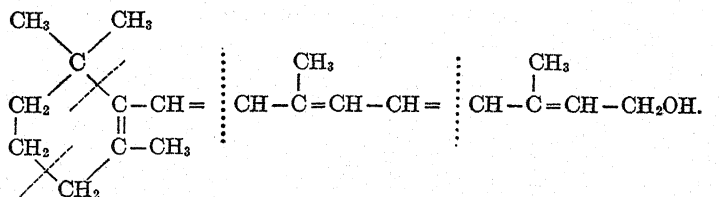
the characteristic grouping — C — C — C — C — C — C — in the middle of the molecule.

**Cryptoxanthine and xanthophyll** appear to be closely related to carotene. They contain two alicyclic rings and eleven double bonds. In cryptoxanthine there is an hydroxyl group on one of the alicyclic rings, and in xanthophyll there are two hydroxyl groups, one on each of the two rings.

**Color of Polyene Pigments.** The color of the polyene pigments is due to the occurrence of a number of double bonds in a conjugated system. The greater the number of such bonds, the deeper the color; thus, crocetin with 7 is yellow, while carotene with 11 is red. The synthesis of a series of substances of the general formula  $C_6H_5(CH=CH)_n C_6H_5$  has shown the relation between the color and an accumulation of double bonds in a conjugated system.

**Vitamin A.** Vitamin A and vitamin D (p. 501) are the so-called "fat-soluble" vitamins. This name originated from the fact that they were first found associated with the fats. The absence of vitamin A in an otherwise satisfactory diet leads to a state of ill-health which is characterized by a degeneration in the structure of the eye, a condition known as xerophthalmia.

Vitamin A has been isolated from the "unsaponifiable residue" (p. 183) from fish oils. The structural formula shows that it is closely related to beta carotene and like this substance can be regarded as made up of isoprene residues (indicated by dotted lines in the formula below:



The close relation of vitamin A to carotene had been proved before the isolation of the vitamin itself. It was shown that either alpha or beta carotene could replace vitamin A in the diet of animals; the carotene was transformed to vitamin A in the liver. More recently it was demonstrated that gamma carotene and cryptoxanthine could also replace the vitamin in the diet. The four carotenoids may thus be called pro-vitamin A.

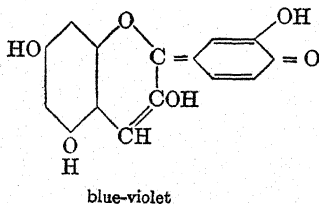
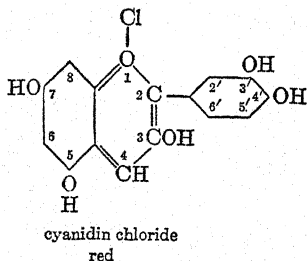
Vitamin A is colorless but has a characteristic absorption in the near ultra-violet, and this fact has greatly aided the investigators. Ultra-violet

absorption spectra of various fats and oils give valuable information about the presence of vitamin A. The five (or perhaps six) conjugated double linkages in the vitamin are sufficient to place the maximum of light absorption in the near ultra-violet, but there are not quite enough conjugated linkages to move the absorption into the visible region and produce a colored compound (compare Fig. 33, p. 544). Like all substances with a series of conjugated double bonds, vitamin A gives an intense blue color when treated with antimony trichloride in chloroform solution. This test has been standardized as a quick method of estimating the vitamin A content of medicinal preparations; the results are expressed in terms of "blue values" (B.V.). This method of assay is clearly open to error if there are other substances present containing conjugated, unsaturated systems.

### ANTHOCYAN PIGMENTS

The brilliant red and blue coloring materials of flowers, fruits, and variegated leaves are usually glucosides of certain phenolic substances which conform to one general type. The glucosides are known as the **anthocyan**s or **anthocyanins**; after removal of the sugar molecules by hydrolysis the resulting colored substance is known as an **anthocyanidin**. The anthocyanins can be extracted from the plant tissue by mixtures of alcohol and water to which a little acid has been added. Both the anthocyanins and anthocyanidins may be obtained in crystalline form.

**Structure of Anthocyanidins.** An investigation of the structure of the anthocyanidins has shown that they all contain the same carbon skeleton and differ only in the number of hydroxyl groups (phenolic groups) or methoxyl groups. The commonest anthocyanidin is **cyanidin chloride**, which has the following structure and which will serve to show the common carbon skeleton:

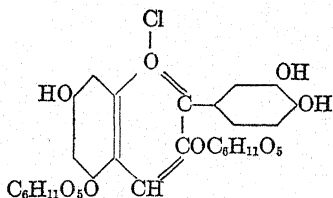


It will be noted that the substance is a chloride, — an oxonium salt. These salts are stable even in essentially neutral aqueous solution. The reason for this great stability of the oxonium

salt is the peculiar aromatic ring which is formed when the oxygen atom increases its valence and takes on salt-forming properties. This phenomenon was discussed in connection with the pyrylium salts (p. 517). In the oxonium salt form, all the anthocyanidins and the corresponding anthocyanins are reddish; when treated with alkali they pass into a blue or violet form which probably contains a quinonoid grouping (lower formula above). On further treatment with alkali, the phenolic hydroxyl group forms a metallic salt which is bluish. The change of the chromophoric group on passing from acid to alkaline solution should be noted.

The other two common anthocyanins found in nature are **pelargonidin chloride** and **delphinidin chloride**. They differ from cyanidin chloride only by the number of hydroxyl groups on the phenyl group attached to the 2 position of the heterocyclic ring. Thus, in pelargonidin chloride there is only one OH group in the 4' position, while in delphinidin chloride there are three in positions 3', 4', and 5'. These differences affect the shade of the color markedly, particularly in acid solution; pelargonidin is orange-red, cyanidin red, and delphinidin bluish red. In still other anthocyanidins, methoxy groups are present in positions 3' and 5'.

**The Color of Flowers.** The anthocyanidins occur in nature combined with one or more molecules of sugar. It has been established that the one sugar molecule is always attached to the hydroxyl group in the 3 position. In addition an hydroxyl group at position 5 may be attached to a sugar residue. Thus cyanin, the diglucoside of cyanidin which occurs in the rose and the blue corn flower, has the following structure:

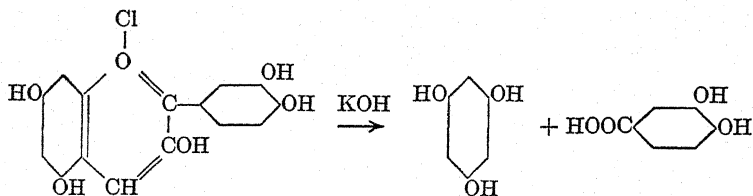


The glucose residues make the compounds much more soluble in water, of course. The anthocyanins occur in solution in the aqueous cell sap (see Fig. 35).

Since the color of the anthocyanidins, and consequently that of

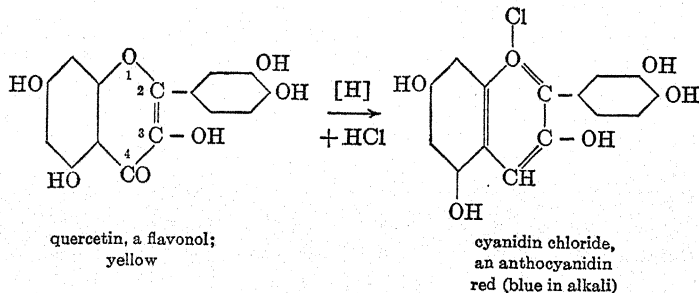
the anthocyanins, changes with alteration of acidity, the same pigment may serve as a reddish or a bluish coloring material. This explains the surprising fact that the same pigment occurs in both the red rose and the blue corn flower. In the rose it is present as an oxonium salt and is reddish; in the corn flower as a potassium or calcium salt and is bluish. It has been found that the color and shade of a flower (or berry) depend on: (1) the anthocyan which is present (mixtures often occur); (2) the acidity of the cell sap; (3) the presence of certain other pigments (yellow flavones) and colorless complex substances which seem to affect the shade (co-pigments).

**Anthocyanidins and Flavonols.** The constitution of the anthocyanidins was first established by fusing the compound with alkali which decomposes the molecule. The nature of the fusion products shows the position of the hydroxyl groups in the molecule. For example,



This formation of phloroglucinol and a di-hydroxybenzoic acid shows the close relation of these pigments to the simple hydroxy aromatic compounds found in nature (see p. 393, for example). Both anthocyanins and many anthocyanidins have been now synthesized in the laboratory by methods which establish even the positions of the glucose molecule.

The flavonols are a group of yellow pigments which occur as glucosides, and are therefore soluble in water. They often occur with the anthocyanins in the cell sap. The relation between them and the anthocyanidins is illustrated by the following transformation which can be brought about in the laboratory and may possibly occur in nature:



The *flavones* are another group of yellow coloring materials occurring as glucosides. They differ from the flavonols only in the presence of a hydrogen atom instead of an hydroxyl group in position 3. The yellow color of the flavones and flavonols is extremely weak and usually masked completely by the anthocyanins or the pigments of the chloroplast. It was at one time thought that the flavones and flavonols were precursors in nature of the anthocyanins. It now seems more probable that some unknown colorless compound is a common precursor of all three types of compounds.

### PYRROLE PIGMENTS

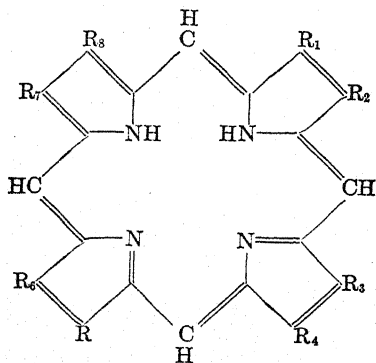
Chlorophyll, the green material involved in the process of photosynthesis, and hemoglobin, the red coloring material of blood, both owe their color to a combination of four pyrrole nuclei joined in a complex molecule. Chlorophyll contains a *magnesium* atom, and hemoglobin an *iron* atom. Both metallic atoms are similarly joined to colored molecules as complex salts. The magnesium is readily removed from chlorophyll by the action of dilute acids; the iron is much more tightly bound in hemoglobin. Both pigments on vigorous reduction by heating with red phosphorus and hydrogen iodide yield a mixture of alkyl pyrroles which are volatile and can be separated. The pyrrole pigments may be defined as colored substances which on reduction yield simple pyrroles.

**Hemin.** When the protein, hemoglobin (p. 585), is treated with hydrochloric acid under suitable conditions, the colored portion of the molecule is split off. In this way, the colorless globin (a protein) and the black, crystalline compound, hemin,  $C_{34}H_{32}N_4O_4FeCl$ , are formed. The iron is in the ferric state in hemin. By the action of reducing agents and acids, the iron may be removed and a purple substance formed. This is the true pigment of hemoglobin and is known as **protoporphyrin**. Its structure has been established by synthesis. The compound is but slightly soluble in organic solvents, but dissolves in acids and alkali, as it is amphoteric. Its solutions in acid have a beautiful purple color.

Protoporphyrin is a representative of a class of pyrrole pigments known as the **porphyrins**. They are characterized by their purple color, their weakly basic properties, and the type of absorption spectrum (p. 544). Unlike most organic compounds, the absorption spectrum *in the visible* of solutions of porphyrins is

composed of a number of relatively narrow bands. The pattern is the same for all porphyrins, but the exact position of the lines is somewhat affected by changes in structure; the metallic compounds such as hemin have a different type of banded spectra. Porphyrins have been found in small quantities in both the animal and plant kingdoms. In certain rare diseases, porphyrins are produced in quantity and excreted in the urine. These porphyrins differ from protoporphyrin in the nature of the groups attached to the group of pyrrole nuclei.

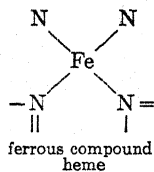
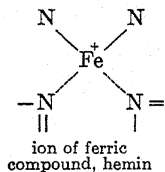
**Structure of the Porphyrins.** All the porphyrins may be considered as derivatives of a parent substance of the following structure in which all the R's are hydrogen:



The parent substance is named **porphin**. In **protoporphyrin**  $R_1$ ,  $R_3$ ,  $R_5$ ,  $R_6$  are methyl groups,  $R_6$  and  $R_7$ ,  $\text{CH}_2\text{CH}_2\text{COOH}$  groups, and  $R_2$  and  $R_4$ , vinyl groups. The porphin ring consisting as it does of four pyrrole nuclei joined together is an essentially aromatic structure. Different arrangements of double linkages can be written without shifting an atom or group. No isomers corresponding to such formulas have ever been found, however. There is undoubtedly a good deal of resonance energy which imparts to the porphin ring a marked stability.

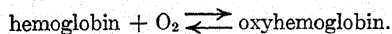
Porphyrins readily form metallic derivatives in which the two hydrogen atoms on two of the four nitrogen atoms are replaced by metal. A model of the porphin ring shows that all four pyrrole rings and connecting  $-\text{CH}=\text{}$  groups lie in a plane. The space between the four nitrogen atoms is thus like a hole in a doughnut in which various metallic atoms readily fit. In some cases the other two nitrogen atoms probably are involved in the linkage by occupying coordination positions (compare the structure of the ferri-

cyanide or cobalt amines). Thus, the central core of the hemin molecule is to be represented as:



Compounds containing rings of the porphin type but with nitrogen atoms ( $\text{—N=}$ ) substituted for the  $\text{—CH=}$  links have been prepared from simple pyrrole compounds. Like the porphyrins they contain a large planar aromatic ring, are highly colored, and form relatively stable, colored, complex metallic derivatives. The compounds in which all four links are  $\text{—N=}$  are known as the **tetra-azoporphyrins**. Substances containing this structure and having phenyl groups as substituents on the pyrrole rings (or fused to the pyrrole rings as in indole) can be prepared from certain aromatic nitriles. They are highly colored and their metallic derivatives which are very resistant to acids are being developed as an important class of dyes and colors. One class of these colors is known as the **phthalocyanines**. It is a matter of considerable interest that a *purely physical method*, the X-ray analysis of the copper derivative of a phthalocyanine and the metal-free parent compound, completely established the arrangement of all the carbon and nitrogen atoms in the molecule. It was possible to determine the complete structure of this complex substance in this instance because of the symmetry of the compounds and their metallic derivatives.

**Hemoglobin.** When hemin is gently reduced, the iron passes from the ferric state to the ferrous state. The resulting compound has been called **heme**. Heme may be combined with the colorless globin carefully prepared from hemoglobin (denaturation must be avoided). The synthetic combination of heme and globin appears to be identical with natural hemoglobin. The iron in hemoglobin is in the ferrous state. Solutions of hemoglobin are purplish (venous blood). When shaken with oxygen they become red (arterial blood), because the hemoglobin combines loosely with the oxygen forming **oxyhemoglobin**. One molecule of oxygen is absorbed for every iron atom in the molecule. The oxygen may be removed by merely lowering the pressure of the gas above the solution:



It is believed that the oxygen molecule is held to the ferrous iron atom of the hemoglobin as a coordination compound by secondary

valence forces. Hemoglobin also combines with carbon monoxide. Since the combination is firmer than with oxygen, small quantities of carbon monoxide will prevent oxygen from attaching itself to hemoglobin. This is the cause of carbon monoxide poisoning. When the iron in the hemoglobin molecule is oxidized to the ferric state, the color of the solution is brown; the ferric compound is known as **methemoglobin**. Methemoglobin combines with neither oxygen nor carbon monoxide; it can be reduced to hemoglobin.

**Bile Pigment.** An orange pigment occurs in the bile which is known as **bilirubin**. It has been shown to be an oxidation product of the porphyrin constituent of hemoglobin, the process involving the formation of a green pigment (**biliverdin**). In this transformation, the protein molecule is first split off from hemoglobin. The heme is changed by an oxidation to an iron derivative of a tetrapyrrole compound in which the porphin ring has been opened. Finally iron is removed yielding bilirubin. Since in bilirubin the four pyrrole nuclei are joined in a chain, the characteristic properties, including the spectra, of porphyrins are absent.

**Chlorophyll.** The two chlorophylls present in the chloroplast are known as chlorophyll *a* and chlorophyll *b*. Their structures differ only by the fact that chlorophyll *b* contains an extra oxygen in place of two hydrogen atoms (*i.e.*, as an aldehydic group). Solutions of both chlorophylls are green. After removing the magnesium atom by the action of acids the solutions are brownish. The four pyrrole nuclei in the chlorophyll molecule are joined together in a ring very similar to that in the porphyrin molecule, but the magnesium-free compounds are not porphyrins; instead, they contain a partially hydrogenated porphyrin nucleus.

Both chlorophylls *a* and *b* have carboxyl groups in the molecule which are esterified; one with methyl alcohol and one with phytol. The phytol is readily removed by hydrolysis.

The role of chlorophyll in the process of photosynthesis still awaits elucidation. This highly colored substance certainly serves to absorb the radiant energy required for the conversion of carbon dioxide to sugar. Whether in addition to this it enters into the chemical reaction as an intermediary is uncertain. Outside the living cell neither chlorophyll nor any other materials which have been obtained in nature are capable of catalyzing the photosynthetic reduction of carbon dioxide. It would appear that a series

of complicated reactions are involved in photosynthesis in which enzymes of different sorts probably play a vital role.

**Porphyrins in Minerals.** Porphyrins have been found in small quantities in shales, petroleum, and asphalts. They have been isolated and their structure established. Those present in largest amounts are clearly derived from chlorophyll; those present in small amounts have a structure which shows their precursor was hemin (presumably hemoglobin). The relative proportion of these two types demonstrates that plant material was much more important than animal material in the origin of petroleum. Several of the porphyrins contain carboxyl groups which rather easily lose carbon dioxide when the substance is heated. The fact that these porphyrin acids are present in petroleum demonstrates that the geological formation of mineral oil must have been an essentially low-temperature process. It is estimated that the oils or minerals which contain these porphyrins could not have been subjected to a temperature of more than 200° at any stage during their formation. The older theories of petroleum formation which postulated a destructive distillation at relatively high temperatures below the earth's surface must be revised.

## CHAPTER XXXIII

### ADVANCED TOPICS IN STEREOCHEMISTRY

#### METHODS OF DETERMINING CONFIGURATION

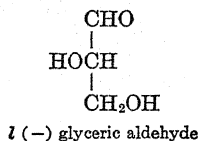
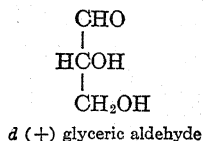
**The Problem.** In Chap. XII it was pointed out that while we could make two models corresponding to dextro and laevo lactic acid (p. 223), it was impossible to decide which model corresponded to one particular isomer. As far as we can tell at present, there is no way of deciding the real or absolute configuration of the groups in an optically active molecule. We can, however, obtain a great deal of information about the configuration of a series of compounds *relative* to the configuration of some other substance. For example, if an optically active ester of lactic acid on hydrolysis yields the dextro acid, the configuration of the groups around the asymmetric atom presumably in the ester must be the same as in the dextro acid. If we choose one model for the dextro acid, we must choose a similar one for the ester. In this simple case the configuration of the ester may be determined *relative* to that of the acid.

It might be imagined that the sign of the rotation would in itself reveal the relative configuration of a series of compounds. Thus, one might assume that if the ethyl ester of lactic acid was dextrorotatory it must be derived from the dextro acid. A great many facts show that such a naive assumption is *not* correct. For example, the lactic acid from muscle (p. 315) is dextrorotatory in solution, but its salts and esters are laevorotatory although the dextro acid may be regenerated from them. In many cases, the sign of the rotation varies with the solvent or even with the concentration of the solution. The latter is the case with the salts of malic acid ( $\text{HOOCCH}_2\text{CHOHCOOH}$ ), while some amino acids which are laevorotatory in water are dextrorotatory in concentrated hydrochloric acid.

Clearly the sign of the rotation is not a sure guide to the relative configuration of even two closely related compounds. The problem, therefore, is to determine the relative configuration of a series

of compounds by interconversions which will not alter the configuration. Certain experiments have shown that such interconversions *must not involve the substitution of an atom or group directly attached to the asymmetric carbon atom.*

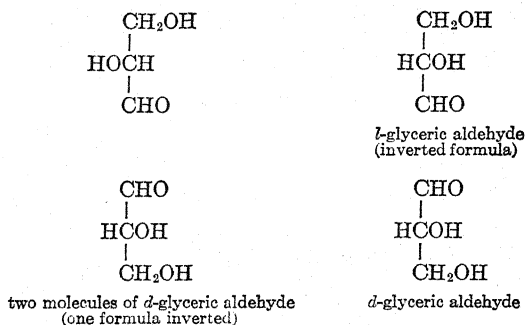
**Conventions Employed.** In order to represent the results of stereochemical investigations, it is necessary to construct models or draw plane projections of such models. It is desirable that the same conventions should be used by all chemists. Since all the configurations which have been determined are relative, it is only necessary to choose arbitrarily one model for one of two optical isomers and relate all substances to this choice. Glyceric aldehyde,  $\text{CH}_2\text{OH}-\text{CHOH}-\text{CHO}$ , is a convenient reference substance; it contains only one asymmetric carbon atom and it has been agreed that the two forms of the aldehyde are to be represented by the following spatial formulas:



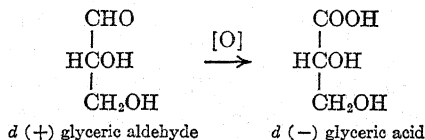
The letters *d* and *l* are used to designate the configurations of a substance relative to this arbitrary choice and irrespective of the sign of rotation. The actual sign of rotation of the substance is shown by the symbols (+) for the right handed and (−) for the left handed. For the reference substance itself the configuration (*d*) and the sign of rotation (+) coincide; for another substance this may or may not be the case.

The reader may be reminded at this time of certain consequences of the projection of three-dimensional models on a plane. Two formulas are identical if a rotation of the paper through  $180^\circ$  in the same plane brings them into coincidence; two formulas are mirror images if folding the paper to bring the printed letters in contact results in superposition. It is usual to write aldehydes with the carbonyl group at the top; if this is done, the projection formula for *d*-glyceric aldehyde has the OH group on the right. The student should convince himself, however, that both the formulas below on the left represent *d*-glyceric aldehyde while of those on the right the upper is *l*-glyceric aldehyde, the lower

*d*-glyceric aldehyde. The construction and handling of three-dimensional models will be of great assistance in an understanding of this whole subject.

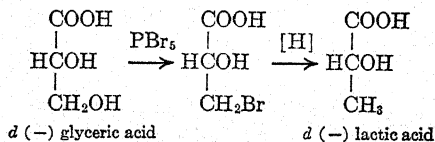


**The Configuration of the Hydroxy Acids.** Glyceric aldehyde is readily oxidized to glyceric acid,  $\text{CH}_2\text{OH} \text{CHOH} \text{COOH}$ . The dextro aldehyde yields an acid with a laevo rotation; here the configuration and the rotation are *opposite*.



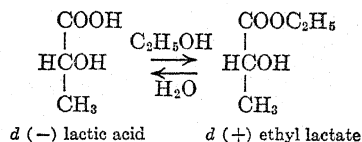
A similar transformation can be accomplished with the laevo form of the aldehyde which yields the dextro form of the acid. Only one such relation need be formulated here, however. It will be noted that the space formula for (-) glyceric acid is perfectly definite after we have once made an arbitrary choice in regard to glyceric aldehyde.

The lactic acid with a laevo rotation is connected with *d* (-) glyceric acid by the following transformations:

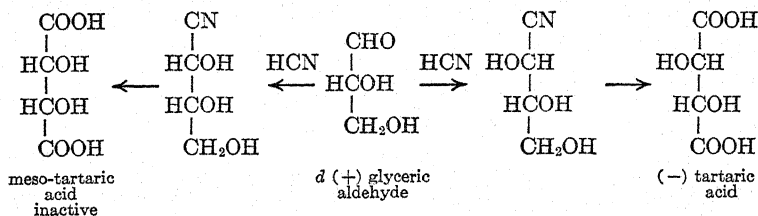


As mentioned earlier the esters of lactic acid have the opposite

sign from the parent acid, so we may write:



**Configurations of Tartaric Acid.** Glyceric aldehyde combines with hydrocyanic acid to form an hydroxy nitrile (p. 117). On hydrolysis and oxidation this yields tartaric acid. From *d* (+) glyceric aldehyde a mixture of meso-tartaric acid and laevo-rotatory acid is formed because in the production of the second (new) asymmetric atom, both a dextro and a laevo configuration are formed as usual. The transformations are to be represented thus:



(The student is advised to review the conventions used in representing tartaric acid by a projection formula (p. 226) and compare with the formulas of glyceric aldehyde shown on page 614.)

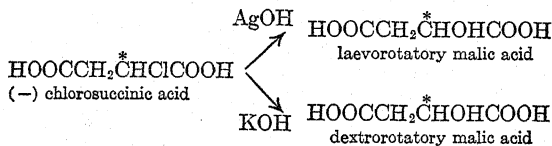
The configuration of the tartaric acids is settled by the transformation just outlined but the question of *nomenclature* is left unsettled. One would expect the laevo tartaric acid to be designated *d* (-) tartaric acid but the name laevo tartaric acid is so imbedded in the literature of stereochemistry that this would be very awkward. For our purposes we shall leave it without a stereochemical designation, it being carefully noted that its *stereochemical formula* (configuration) is clearly settled.

It has been proposed to assign the prefix *d* or *l* to alpha hydroxy acids according to the configuration of the alpha carbon atom. If this convention is agreed to then it is evident that (-) tartaric acid is related to *l* (+) glyceric acid and *l* (+) lactic acid. It therefore becomes appropriate to designate it as *l* (-) tartaric acid and if the COOH group is written at the top, the OH

is on the left for the *l* series, and on the right for the *d* series. It is evident from the difficulty involving tartaric acid that the stereochemical *nomenclature* must be necessarily based on a number of conventions, and is to some extent arbitrary. The stereochemical formulas (configurations) are quite independent of the nomenclature adopted, however, and only depend on *one* arbitrary convention to which all chemists agree.

**Racemization.** Some optically active compounds lose their activity on being treated with certain reagents or on heating (p. 229). This process may occur in the substitution of one group on an asymmetric atom by another group, or may involve merely a change of an optical isomer into a racemic mixture. Racemization is particularly apt to occur if the asymmetric atom is in the alpha position to a carbonyl group and if the atom carries a hydrogen atom. For example, ketones of the type,  $R_1R_2CHCOR$ , are easily racemized by treating with a little alkali. In this instance the process involves the formation of the inactive enol form (p. 238), which then shifts back to an equimolecular mixture of the *d* and *l* keto forms. Optically active acids and their derivatives (esters, amides) of the type  $R_1R_2CHCOOH$  can also be racemized; compounds of the type  $R_1R_2R_3CCOR$  cannot be racemized.

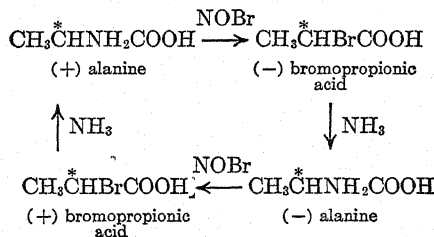
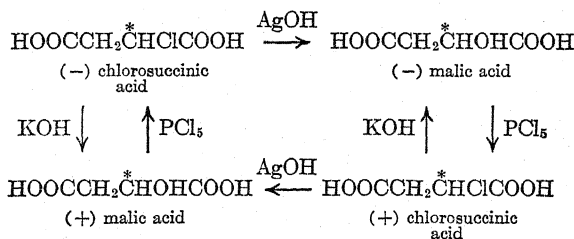
**Walden's Inversion.** As previously noted, the reactions which have been used to establish stereochemical relations have been carefully chosen to avoid disturbance of the groups directly attached to the asymmetric carbon atom. The importance of this restriction was evident early in the development of stereochemistry as a result of the work of P. Walden. This investigator showed that when the chlorine atom in (–) chlorosuccinic acid is replaced by the hydroxyl group, one could obtain either a dextro- or a laevorotatory malic acid depending on the reagent chosen. These important facts are summarized below:



This phenomenon is called **Walden's inversion**. Evidently in one or the other reaction something peculiar had taken place, and the groups around the asymmetric atom had shifted places and

produced the isomer of opposite configuration. It was soon found that similar difficulties were often encountered in a reaction in which a group or atom *directly* attached to the asymmetric carbon atom was replaced by another group or atom. Thus, if one of the valence bonds of the asymmetric carbon atom were broken in a reaction, there was no guarantee that the configuration of the new compound would be the same as that of the initial material. On the other hand, if the bonds of the *asymmetric carbon atom are not involved in a reaction*, *Walden's inversion does not take place*. This latter fact, based on countless experiments, has made possible the determination of configuration by the methods outlined in the preceding paragraphs.

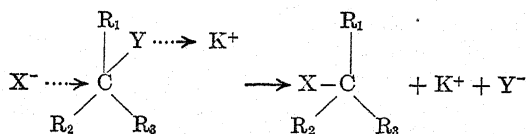
The following diagrams summarize a number of reactions in which Walden's inversion has been studied. Such cyclic processes show that at one stage or another a Walden inversion has occurred; each half of the cycle represents the conversion of one enantiomorph into the other:



It must be carefully noted that there is no way of telling from the data given above in which one of the substitution reactions a stereochemical inversion has occurred. This would only be possible if we had some independent way of determining the configuration of the products.

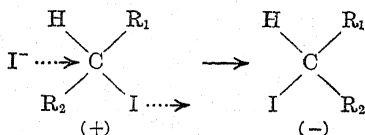
**Problems Raised by Walden's Inversion.** From what has been previously said, it is evident that one can not tell merely from the sign of the rotation whether an optical inversion has occurred or not. Thus, there is no simple way of determining whether silver hydroxide or potassium hydroxide yields an hydroxy acid with the same configuration as chlorosuccinic acid. For many years, there has been the difficult problem of deciding which substitution reactions involving the asymmetric atom were normal and which abnormal (*i.e.*, produced an optical inversion).

The second problem raised by Walden's inversion is in regard to the mechanism by which such an inversion may occur. Clearly at that step in process where the configuration changes, the entering atom or group must attach itself to the asymmetric carbon atom on the side *opposite* the atom or group which is being replaced. If the attachment were at random to the one side or the other, the product would be inactive, of course (*i.e.*, racemization would occur). This does not happen, however, so there must be some force directing the substitution. It has been suggested that this force is essentially electrical, at least, when the entering group is a negative ion. According to this view, the group or atom being removed is attracted by the positive ion and the negative ion approaches the molecule from the opposite side. Thus:



**Mechanism of Substitution Reactions.** It has been demonstrated that certain types of substitution reactions do involve a stereochemical inversion and probably proceed according to the scheme just outlined. These are the reactions in which an alkyl halide reacts with a negative halogen ion. It will be recalled that an alkyl chloride or bromide reacts with an inorganic iodide to yield an alkyl iodide (p. 26). In these reactions one halogen atom is replaced by another. A halogen atom will also interchange with the negative ion of the *same* halogen. This has been established by using an inorganic iodide containing radioactive iodine (the radioactive isotope) and allowing this salt to interact with an

alkyl iodide. The speed with which the alkyl iodide became radioactive is clearly the speed of the reaction,  $RI + I' \longrightarrow RI' + I$ . Now it was known that an *optically* active iodide  $R_1CHIR_2$  underwent rather rapid racemization in a solution of an inorganic iodide. The rate of this racemization was the same as the rate of introduction of radioactive iodine into the same halide when a radioactive iodide was employed. This establishes the fact that the racemization in this case involves the interchange of the iodine atom of the organic molecule with the iodine atom of the iodine ion. Racemization could only occur in this reaction if the entering atom occupied the position *opposite* to that held by the halogen atom which departs.



Clearly when half of the molecules had reacted in this manner, the compound would be optically inactive. Although the same reaction would continue in solution, just as many  $(-)$  molecules would be converted to  $(+)$  as  $(+)$  to  $(-)$ .

Arguing by analogy, it has been concluded that whenever an organic halide reacts with a negative ion, stereochemical inversion occurs. This seems reasonable on theoretical grounds as it would be expected that the halogen atom with its complete shell of electrons would repel a negative ion. The ion would therefore be attracted by the carbon atom to the *opposite* side of the molecule. The further fact that in metathetical reactions of this type the speed of the reaction decreases in the order primary halide  $>$  secondary halide  $>$  tertiary halide, is readily explained. The approach of the negative ion to the side opposite to the halogen atom is hindered by the larger groups (steric hindrance) in the case of the secondary and tertiary halides. In the hydrolysis of alkyl halides, on the other hand, which does not proceed by a mechanism involving a negative ion the order of reactivity is reversed; in this case tertiary halide  $>$  secondary halide  $>$  primary.

**Determination of Configuration.** When Walden's inversion was first discovered, efforts were made to determine which of the two

steps was "abnormal" (*i.e.*, involved inversion) by considering the sign of rotation of the reactant and product in each step. Though it is evident that the change of sign alone did not prove that an inversion occurred, nevertheless it was assumed by some chemists that in the majority of cases, the compounds of the same sign would have the same rotation. A statistical survey of substitution reactions involving optically active compounds then showed that in general, certain reagents yielded products with the same sign as the reactant while other reagents usually gave products with an opposite sign. The first group might be considered to bring about substitution without inversion, the second to cause inversion. As a first approximation, this method of approach to the problem was not without value but it clearly was unreliable in any specific case.

Later attempts were made to solve the problem by essentially physical methods. It was hoped that the configuration of a compound could be determined by measuring the direction and amount of the rotation at different wave-lengths not only of the substance itself but also closely related derivatives (prepared by reactions which did not involve the asymmetric atom). This method has not as yet proved entirely satisfactory, however.

Finally, since the demonstration that stereochemical inversion does, indeed, occur in one type of reaction, attention has been directed to the kinetics of substitution reactions in general. It is hoped that by discovering what type of reaction is involved in each case it may be possible to decide whether or not inversion occurs. For example, since the reaction  $RI + I' \longrightarrow RI' + I$  does involve inversion it is safe to assume that  $RCl + I' \longrightarrow RI' + Cl$  does also and probably that  $RBr + AgOOCCH_3 \longrightarrow ROOCCH_3$  does also. If a (+) bromide yields a (-) acetate, we know the sign is in this case a correct measure, for an inversion has occurred. From such an acetate we can obtain the alcohol by hydrolysis and without affecting the asymmetric atom. In this way it has been established that alcohols, esters, and halides of the type,  $CH_3CHX-C_nH_{2n+1}$  (where  $X = OH, Cl, Br, I, \text{ or } OOCCH_3$ ) all have the same configuration if they have some sign of rotation. Finally from the observation that a halogen acid converts an alcohol to a halide without a change of sign, it is clear that this reagent, unlike the

alkali halides or salts of acids, brings about substitution without inversion. The application of this general point of view to other cases will be evident from this example. Whether or not all the cases of Walden inversion can be settled or not by this line of attack is not yet certain. The fact that in certain instances, the same reaction yields a product with a different sign of rotation depending on the conditions (*e.g.*, solvent) illustrates the difficulties of generalizing from a few instances.

**Asymmetric Molecules without Asymmetric Atoms.** In our first discussion of optical activity (p. 225) it was pointed out that two mirror images are possible if the molecule is asymmetric. Optical activity is a property of an asymmetric *molecule*. In most cases such asymmetric molecules contain one or more asymmetric carbon atoms and it is usually most convenient to focus the attention on these asymmetric atoms. However, it often happens that by regarding the molecule as a whole and deciding whether it is symmetrical or asymmetrical, it is possible to decide at once as to whether or not it can be optically active. The trihydroxyglutaric acids to be considered shortly are such an instance. In dealing with complex cyclic compounds this point of view is particularly useful.

It is very easy to construct models of several types of organic compounds in which there is no asymmetric atom and yet the molecule as a whole is asymmetric. The simplest example of this

is a tetra-substituted allene: 
$$\begin{array}{c} \text{R}_1 \\ \diagdown \\ \text{C} = \text{C} = \text{C} \\ \diagup \\ \text{R}_2 \end{array} \begin{array}{c} \text{R}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}_4 \end{array} .$$
 A model of

this compound shows that the *molecule* is asymmetric. This is a good example of an asymmetric molecule which does not contain an asymmetric atom. Such molecules have been resolved.

**Asymmetric Diphenyl Compounds.** A number of rather complicated compounds have been resolved in which there is no asymmetric atom. A special group of such substances in which the asymmetry is the result of a restricted rotation has been discovered and thoroughly investigated. A substituted diphenic acid (p. 465) will serve as an example. Ortho nitrodiphenic acid can be resolved into a dextro and laevo form by the usual methods. The free

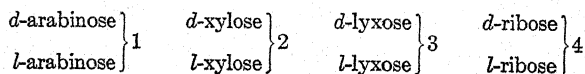
rotation of the two phenyl groups around their common axis is prevented by the large carboxyl and nitro groups in the ortho positions. The planes of the two rings are thus kept at approximately *right angles* as shown below. Such a molecule is asymmetric and can exist in the two forms indicated.



Many examples of this type of asymmetric molecule are known. Whether or not an unsymmetrical diphenyl can be resolved clearly depends on whether or not the rotation around the bond joining the two aromatic nuclei is restricted. It has been shown that this depends on the size of the atoms or groups in the ortho position which collide and block rotation if they are large enough. Thus, four fluorine atoms will not block free rotations, and an unsymmetrical diphenyl with these four atoms in the ortho position is not resolvable into enantiomorphs. When two fluorine atoms and two carboxyl groups are present the compound is resolvable but it rapidly racemizes.

### THE CONFIGURATION OF THE SUGARS

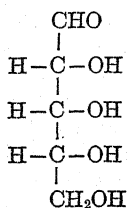
**The Configuration of the Pentoses.** The methods first employed for determining the stereochemical formulas for the monosaccharides may be best illustrated by considering the aldopentoses. We shall here use the open-chain aldehyde formula, bearing in mind its true relation to the cyclic formula of the sugars and glucosides (p. 307 and p. 312). There are three asymmetric carbon atoms in the aldopentoses, and therefore  $2^3$  or 8 stereoisomers. These may be divided into four pairs of enantiomorphs; the two members of each pair will differ only in the sign of their rotation. All of the eight possible isomers are known and have the following names:



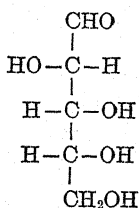
The problem is to study the transformations of these eight sugars, and thus assign to each of them the proper stereochemical

formula. Fortunately, this can be done without involving a substitution reaction in which Walden's inversion might occur, and without involving racemization. The absence of these two complicating factors made possible a correct elucidation of the stereochemistry of the sugars very soon after van't Hoff's theory was first proposed.

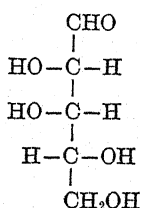
**Four Pairs of Enantiomorphs.** The eight possible stereochemical configurations of the aldopentoses are given below, the formulas being arranged in pairs corresponding to dextro and laevo enantiomorphs. At first it will be necessary only to consider which pair of formulas corresponds to a given sugar.



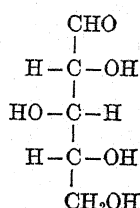
I  
*d*-ribose



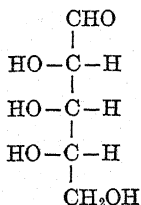
II  
*d*-arabinose



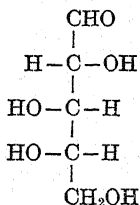
III  
*d*-lyxose



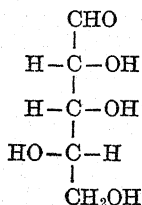
IV  
*d*-xylose



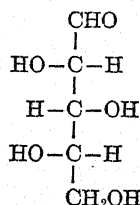
Ia  
*l*-ribose



IIa  
*l*-arabinose



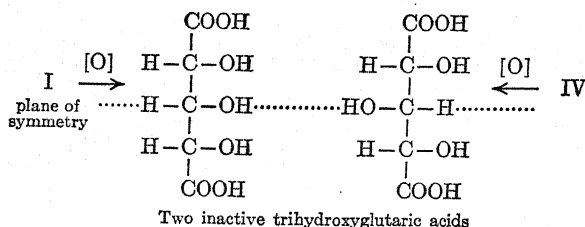
IIIa  
*l*-lyxose



IVa  
*l*-xylose

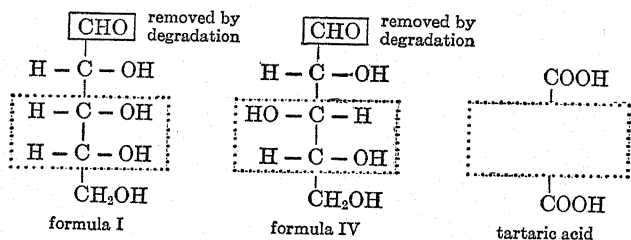
All the aldopentoses may be oxidized to trihydroxyglutaric acids, of the general formula,  $\text{COOHCHOHCHOHCHOHCOOH}$ . Inspection of formulas I-IV makes it evident that if this transformation is carried out with I and IV, an inactive, internally compensated acid will result. These two trihydroxy acids would be inactive for the same reason that mesotartaric acid is inactive; the two carbon atoms next to the carboxyl group are of the opposite configurations and compensate each other. The

molecule is symmetrical and *not* asymmetrical and therefore can not exist in an active modification.



On the other hand, oxidation of compounds with formulas II and III would yield optically active trihydroxyglutaric acids.

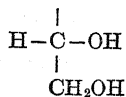
**Configuration of Xylose and Ribose.** Now as a matter of fact, two aldopentoses, xylose and ribose, do yield optically inactive dibasic acids (internally compensated) when they are vigorously oxidized. These sugars therefore correspond to either I (Ia) or IV (IVa), and we must next decide between the two possibilities. This can be done by virtue of the fact that the sugar known as xylose can be degraded to an optically active tartaric acid. This is only possible in the case of a compound with formula IV, since formula I contains only an inactive (meso) tartaric acid grouping.



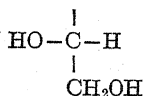
The portion of the molecule enclosed by the dotted square becomes the center portion of the tartaric acid molecule.

The formula of xylose is therefore either IV or IVa and the distinction between these possibilities rests on the arbitrary convention in regard to the *d* and *l* series which we have previously discussed at some length. Clearly the bottom part of formula IV corresponds to the formula adopted for *d*-glyceric aldehyde (p. 613) while IVa corresponds to that for *l*-glyceric aldehyde. It

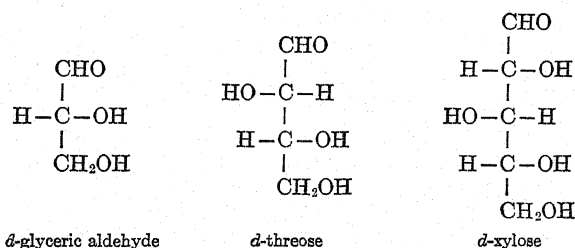
has been agreed to designate by the letter *d* all formulas in the sugar series which have the grouping:



and consider the enantiomorphs with the group



as in the *l* series. Therefore, formulas I-IV are of the *d* series and IV is that of *d*-xylose. Now the form of xylose which happens to rotate to the right ( $[\alpha]_D = +19^\circ$ ) and which results from the hydrolysis of wood can be shown to be related to *d*-glyceric aldehyde while the enantiomorph ( $[\alpha]_D = -19^\circ$ ) is related to *l*-glyceric aldehyde. Therefore, the natural form of xylose is *d*-xylose (formula IV). This relationship is established by degrading *d*-xylose to the aldotetrose, *d*-threose (method of degradation, p. 306), which is oxidized to the same optically active acid (laeo-tartaric acid) as is obtained from *d*-glyceric aldehyde (p. 614). We may therefore write the configurational series:

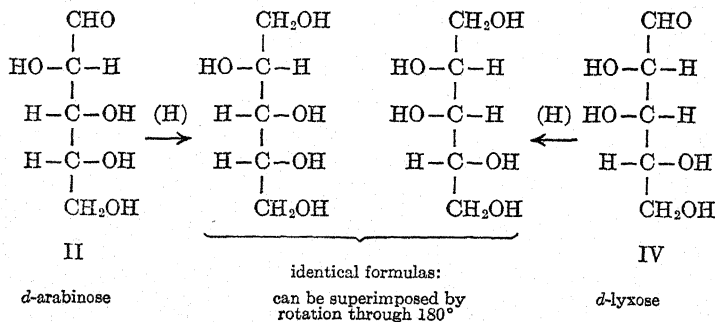


The assignment of a *d* or *l* configuration to natural ribose will be postponed until we have considered the two aldopentoses which yield *active* trihydroxyglutaric acids on oxidation.

**Configuration of Lyxose and Arabinose.** One of these aldopentoses when treated with phenylhydrazine gives the same osazone as *d*-xylose. It must have the same configuration therefore in regard to the lower part of the molecule and differ only in

regard to the spatial arrangement around atom 2. It is epimeric (p. 301) with *d*-xylose. An inspection of the formulas on p. 623 shows that this sugar must be assigned formula III; it is *d*-lyxose.

The other sugar which gives an optically active trihydroxyglutaric acid is arabinose. One of the enantiomorphs of this sugar occurs widely distributed in nature (p. 302), the other can be prepared in the laboratory from glucose by a series of reactions. The only remaining formulas are II and IIa and it is only a question, of assigning these to the synthetic and natural arabinose. This is easily settled by reducing the synthetic sugar to the corresponding alcohol, arabinitol. If formula II is correct, the reduction product will be identical with that obtained from *d*-lyxose (formula IV). This relationship, at first sight obscure, is easily seen if the formula of the alcohol ("itol") from lyxose is rotated through 180°, as illustrated below:

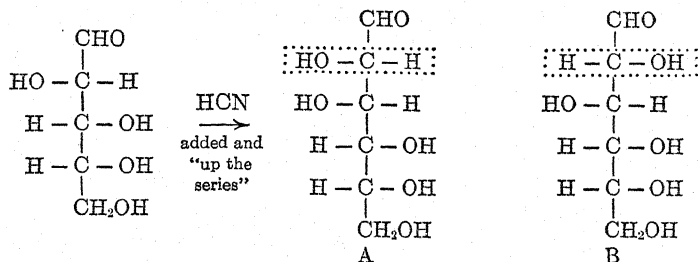


The synthetic arabinose from glucose yields an arabinitol identical with that obtained from *d*-lyxose; it is, therefore, *d*-arabinose (II). The enantiomorph, *l*-arabinose (IIa), is the common arabinose obtained by hydrolyzing many natural gums.

We can now settle the question of whether natural ribose is a *d* or *l* sugar (I or Ia). Natural ribose gives the same osazone as *d*-arabinose (*i.e.*, is an epimer of *d*-arabinose); it is therefore *d*-ribose and is represented by formula I.

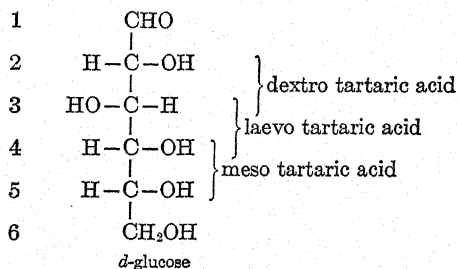
**Configuration of Glucose.** By starting with *d*-arabinose, II, and adding one more carbon atom to the skeleton (p. 305), a mixture

of two aldohexoses is formed. These two sugars are the epimeric pair, *d*-glucose and *d*-mannose (p. 301). The formula of these compounds is thus established as being either A or B below.



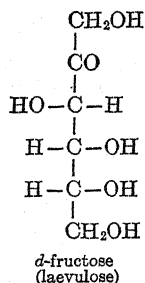
(new asymmetric atom indicated by dotted enclosure)

To decide which of these is mannose and which glucose several different lines of evidence may be presented. The simplest starts from the fact that by oxidative degradation, it is possible to convert *d*-glucose into either meso tartaric acid (removing atoms 1 and 2), dextro tartaric acid (removing 5 and 6), or laevo tartaric acid (removing 1 and 6). An inspection of formula A shows that it does not contain a pair of atoms which could provide the center for a molecule of *dextro* tartaric acid. Formula B, on the other hand, does contain such a grouping (atoms 2 and 3). This is illustrated by the following diagram:



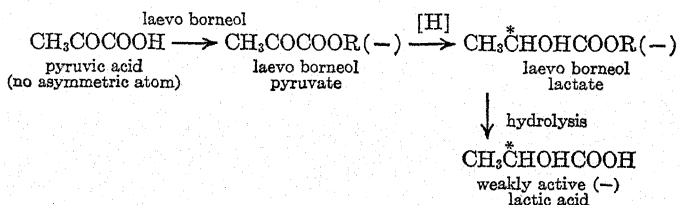
**Configuration of Other Sugars.** The configuration of the six remaining pairs of aldohexoses has been determined by methods similar to those which have been illustrated by our study of the aldopentoses. The stereochemical formula of the ketohexose, *d*-fructose, follows from the fact that it yields the same osazone as

*d*-glucose and *d*-mannose (p. 304). Its formula is, therefore, as follows:



#### THE SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS FROM INACTIVE MATERIAL

When a substance containing an asymmetric carbon atom is produced in the laboratory in the ordinary way, an inactive material always results (p. 228). Since there is an equal chance of the dextro or laevo form being produced, a racemic mixture is formed. On the other hand, in the synthesis of compounds in plants and animals the products are almost always active, if they contain one or more asymmetric carbon atoms. A little light on the possible mechanism of such biochemical syntheses has been thrown by the discovery that it is possible to synthesize an optically active compound in the laboratory by certain procedures. Such an **asymmetric synthesis** can be sometimes accomplished by attaching an optically active molecule to the initial compound, and then removing it after the new asymmetric atom has been produced. The presence of the optically active component often directs the synthesis, so that the final material is itself active. For example, a lactic acid of weak laevo rotation may be synthesized by reducing an optically active ester of pyruvic acid, and then removing the optically active alcohol group.



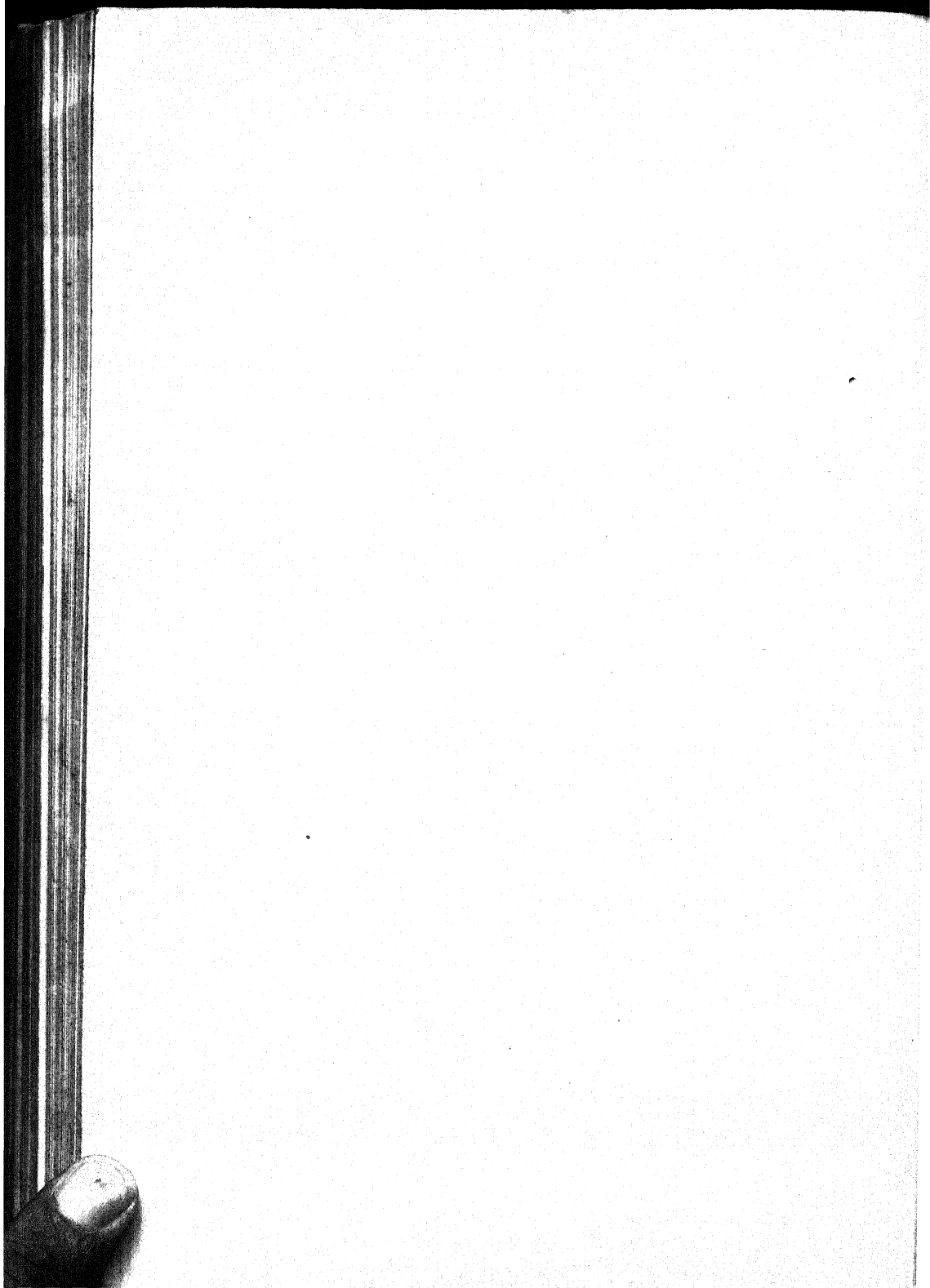
If an inactive ester of pyruvic acid be similarly reduced, the resulting lactic acid is completely inactive, of course. In this instance the presence of the optically active R group attached to the carboxyl in some way causes a greater production of one enantiomorph than the other.

In nature the syntheses are catalyzed by enzymes which themselves are probably optically active. It has been supposed that these enzymes unite with the initial material, and thus direct the production of any new asymmetric atoms formed in the synthesis. After the synthesis is complete, the enzyme and product separate, and the enzyme is free to participate in a new synthesis. The asymmetric syntheses in the laboratory are thus, perhaps, a crude model of the way optically active compounds are formed in nature. In the natural processes, the optically active enzymes are usually so efficient that only one optically active form is produced.

**Absolute Asymmetric Synthesis.** According to the hypothesis just outlined, it is easy to imagine how living things have continued to produce optically active materials, if *once they started with optically active enzymes*. It is probably not profitable at present to pursue the further question of how the first optically active enzyme arose. We are very little informed about the origin of life or the sequence of chemical reactions which were involved in the first biochemical synthesis.

Since the light of the moon or that reflected from the sea is circularly polarized, it is interesting that it has recently been shown that optically active material may be prepared by the action of circularly polarized light on certain inactive compounds. A racemic mixture is employed which is decomposed by the absorption of light (visible or near ultra-violet). The group which is responsible for this absorption must be attached to the asymmetric carbon atom. By using circularly polarized light of the wave-length corresponding to the absorption of this group, one of the enantiomorphs absorbs more light than the other, and therefore more of it is decomposed; the material that is left after radiation is slightly optically active. By using light polarized circularly in the opposite direction the reverse effect is produced and the optical activity of the product is of the opposite sign.

It has been suggested that the origin of optical activity in living things was caused by the action of the circularly polarized light reflected from some surface. Although the experiments just mentioned show that optical activity may arise in certain special cases by such a method, there is no evidence to indicate that such processes are at work in nature now or have been involved in the remote past. The problem of the origin of optical activity must be considered quite unsolved.



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